UNIVERSIDADE DE LISBOA

FACULDADE DE FARMÁCIA

LESSONS LEARNED ON THE SAFETY OF GLP-1 RECEPTOR AGONISTS FROM POST-MARKETING EXPERIENCE

Andreia Filipa Rodrigues dos Santos

Dissertation oriented by Beatriz Lima, PhD

and co-oriented by Ana Paula Martins, PhD

Master's degree in Regulation and Evaluation of Medicines and Health Products

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List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
BID	Administration Twice a Day
cAMP-GEFII or Epac 2	cAMP-Regulated Guanine-Nucleotide Exchange Factor II
CV	Cardiovascular
DM	Diabetes Mellitus
DPP-4	Dipeptidyl-Peptidase 4
EEA	European Economic Area
EGF-R	Epidermal Growth Factor Receptor
ELIXA	Evaluation of Lixisenatide in Acute Coronary Syndrome
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERK	Extracellular Regulated Kinase
EU	European Union
FAERS	FDA Adverse Events Reporting System
Fc	Heavy chain fragment
FDA	U.S. Food and Drug Administration
GI	Gastrointestinal
GIP	Glucose-Dependent Insulinotropic Polypeptide
GLP-1	Glucagon-Like Peptide-1
GLP-1R	Glucagon-Like Peptide-1 Receptor
GPCR	G Protein-Coupled Receptor
IgG4	Immunoglobulin G4
HLGT	High-Level Group Terms
INR	International Normalisation Ratio
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
LLOQ	Lower Limit of Quantification
MAH	Marketing Authorisation Holder
MAPK	Mitogen-Activated Protein Kinase
mcg	Micrograms
MedDRA	Medical Dictionary for Regulatory Activities
MRHD	Maximum recommended human dose
PFS	Prefilled syringe
PI3K	Phosphatidylinositol-3 Kinase
PKA	Protein Kinase A
PKCζ	Protein Kinase Cz
PLG	poly(D,L-lactide-co-glycolide)
PPAR-γ	Peroxisome Proliferator-Activated Receptor Gamma
PRAC	Pharmacovigilance Risk Assessment Committee
QW	Weekly Administration
REMS	Risk Evaluation and Mitigation Strategy
RMP	Risk Management Plan
SC	Subcutaneous
SGLT2	Sodium glucose co-transporters 2
SmPC	Summary of the Product Characteristics
SOC	System Organ Class

SU	Sulphonylurea
T2DM	Type 2 Diabetes Mellitus
THIN	The Health Improvement Network
TZD	Thiazolidinedione
U.S.	United States of America
WHO	World Health Organization

Thesis Outline

The main goals of the present work are drawing a safety profile for Glucagon-Like Peptide-1 receptor (GLP-1R) agonists, namely BYETTA, BYDUREON, VICTOZA, LYXUMIA, EPERZAN and TRULICITY (European Union's names), and conclude about the need and/or opportunity of adapting the Risk Management Plan (RMP) for the new markets, taking into account the safety data collected both in European Union (EU) and United States of America (U.S.).

The thesis is divided in three main parts:
Part I consists of a general introduction organized in three subtopics, one focusing on the disease and its epidemiology, the second presents the therapeutic options available at the moment, and the third one, passing by the pharmacology and distribution of the GLP-1R, presents an overview of the GLP-1R agonists approved and their mode of action.
Part II comprises the methodology and results obtained through this work, which are presented as a comparative analysis between data found in nonclinical and clinical developmental plan, which are compiled in the RMP. Additionally, it is presented a comparison of safety concerns considered by European Medicines Agency (EMA) and those ones identified by U.S. Food and Drug Administration (FDA).
Part III presents a general discussion and the final remarks of all the results obtained throughout this work.

Abstract

Diabetes Mellitus (DM) is one of the most important diseases at public health level around the world.
Over the last 25 years there has been a dramatic increase in the number of people with diabetes around the world. In Portugal, in 2014 the estimated prevalence of Diabetes in population with ages between 20 and 79 years was 13.1%, i.e. more than 1 million of Portuguese people in this age range had Diabetes. During the last decade, in Portugal, it has been observed a significant decrease in the number of potential years of life, lost by DM. Diabetes assumes a preponderant role in the causes of death, and it was the cause of 4.0% of deaths occurred in 2014.

The treatment of diabetes has come a long way in the last century. Starting with the discovery of insulin in 1921, it has seen also the development of antidiabetic drugs. In recent years, newer drugs have become available, targeting specific components of the spectrum of pathophysiologic abnormalities, regulating glucose input, and also addressing glucose utilization and disposal through impacts on insulin resistance and insulin deficiency. The Glucagon-Like Peptide-1 receptor (GLP-1R) agonists mimic the GLP-1 function in order to enhance insulin secretion after food-intake, restoring the incretin function, while being protected from the DPP-4 deactivation. This is achieved by binding to a GLP-1R that resides in the β-cell.

This work focused on drawing a safety profile for GLP-1R agonists and conclude on the need and/or opportunity of adapting their Risk Management Plans (RMPs) for the new markets, taking into account the safety data collected both in EU and U.S..

The methodology herein used was based on the comparison nonclinical and clinical data and RMPs for each medicinal product. Following this, it was presented a resume table identifying the risks considered by European Medicines Agency (EMA) and those ones accepted by U.S. Food and Drug Administration (FDA). After that, a comparison of adverse reactions reported both in European Union (EU) and U.S. within each medicinal product was performed.

It was concluded that the relevant safety information identified in the nonclinical phase was assessed and observed during the clinical phase. The results obtained from all the nonclinical and clinical studies were resumed in the RMP. When observing the post-marketing data, collected from the public databases of adverse reactions reports, it was realized that, although some exceptions, the risks identified previously were the ones mostly reported. In general, the safety concerns identified were similar to all GLP-1R agonists.
Regarding the European and the U.S. data several discrepancies were identified, namely on what concerns to the malignancies occurrence.
It became clear that the occurrence of adverse reactions was associated both to the pharmaceutical formulation of the medicinal products and to their mechanism of action.
Although there are some areas of special concern which require further and thorough analysis (namely the occurrence of cardiovascular (CV) adverse effects and thyroid or pancreatic cancers), it was concluded that all safety concerns are very well monitored and followed either by the EMA/FDA or by the Marketing Authorisation Holders (MAHs).
As final conclusion, it was clear that the safety profile of GLP-1R agonists remain

unchanged after this evaluation and no additional minimisation measures, other than those already defined and implemented, seem to be necessary, and, therefore, the RMPs do not need to be updated.

Key words: GLP-1R agonists, BYETTA, VICTOZA, BYDUREON, LYXUMIA, ADLYXIN, EPERZAN, TANZEUM, TRULICITY, adverse reactions.

Resumo

A Diabetes Mellitus (DM) é uma das doenças mais importantes para a saúde a nível mundial.

Durante os últimos 25 anos houve um aumento dramático no número de pessoas com diabetes em todo o mundo. Em Portugal, em 2014 a prevalência estimada de Diabetes na população com idades compreendidas entre os 20 e os 79 anos era de 13.1%, isto é, mais de 1 milhão de Portugueses nesta faixa etária tinham Diabetes. Durante a última década, em Portugal, houve uma redução significativa do número de anos de vida, perdidos devido à DM. A Diabetes assume um papel preponderante entre as causas de morte, sendo a responsável por 4% das mortes ocorridas em 2014.

O tratamento da diabetes percorreu um longo caminho no século passado. Começando com a descoberta da insulina em 1921, tendo-se também assistido a um grande desenvolvimento de medicamentos antidiabéticos. Nos últimos anos, novos medicamentos ficaram disponíveis, cujos alvos são componentes específicos do espectro das deficiências fisiopatológicas, regulando a entrada de glicose e também a utilização e eliminação de glicose através de ações na resistência à insulina e deficiência de insulina. Os agonistas do recetor do peptídeo-1 semelhantes ao glucagon (GLP-1R) imitam a função do GLP-1 de modo a aumentar a secreção de insulina após a ingestão de alimentos, restaurando a função incretina, enquanto são simultaneamente protegidos da desativação pelo DPP-4. Esta ação é alcançada pela sua ligação ao GLP-1R que se encontra na célula β.

Este trabalho focou-se no desenho de um perfil de segurança para os agonistas do GLP-1R com vista a apurar a necessidade de adaptação dos Planos de Gestão de Risco (RMPs) aos novos mercados, tendo em conta os dados de segurança recolhidos na Europa (EU) e nos Estados Unidos (U.S.).

A metodologia utilizada baseou-se na comparação dos dados não-clínicos e clínicos com os RMPs para cada medicamento. Apresentou-se em formato tabelar um resumo dos riscos considerados pela Agência Europeia do Medicamento (EMA) e os riscos aceites pela *U.S. Food and Drug Administration* (FDA). Após esta abordagem, foi realizada uma comparação entre as reações adversas reportadas na EU e nos U.S. para cada um dos medicamentos.

Concluiu-se que a informação de segurança relevante identificada na fase não-clínica foi avaliada e observada durante a fase clínica. Os resultados obtidos nos estudos não-clínicos e clínicos foram resumidos no RMP. Pela observação dos dados pós-marketing, obtidos a partir das bases de dados públicas de notificações de reações adversas, concluiu-se que, apesar de algumas exceções, os riscos identificados anteriormente são os mais reportados. Em

geral, os problemas de segurança identificados são semelhantes para todos os agonistas GLP-1R.

Relativamente aos dados da EU e dos U.S., várias discrepâncias foram detetadas, nomeadamente no que se refere à ocorrência de tumores.

Tornou-se evidente que a ocorrência de reações adversas está dependente quer da forma farmacêutica dos medicamentos quer do mecanismo de ação dos mesmos.

Embora existam várias áreas de especial atenção que requerem mais e minuciosa análise (nomeadamente a ocorrência de efeitos adversos cardiovasculares (CV) e de cancros da tiroide e pancreáticos), considera-se que todos os problemas de segurança estão bem monitorizados e seguidos tanto pela EMA/FDA como pelos titulares de autorização de introdução no mercado (MAHs).

Como conclusão, percebeu-se que o perfil de segurança dos agonistas GLP-1R permaneceu inalterado após esta avaliação. Deste modo, não parece ser necessário propor novas medidas de minimização de risco, para além das já definidas e implementadas, pelo que não é necessário atualizar os RMPs.

Palavras-chave: Agonistas GLP-1R, BYETTA, VICTOZA, BYDUREON, LYXUMIA, ADLYXIN, EPERZAN, TANZEUM, TRULICITY, reações adversas.

Table of Contents

List of Charts

List of Figures

List of Tables

INTRODUCTION

I. Diabetes

Diabetes Mellitus (DM) is one of the most important diseases at public health level around the world, as it is one of the most common no transmissible disease and it could lead to the development of diverse and severe chronic complications.

Over the last 25 years there has been a dramatic increase in the number of people with diabetes around the world [1].

According to Beaser [2], over 21 million people in U.S. have DM, and this number continues to increase at the rate of about 1 million new patients diagnosed every year. Diabetes hits every age, ethnicity, and socioeconomic status.

According to International Diabetes Federation (2009), the worldwide prevalence for diabetes in 2010 was 285 million, which represented 6.4% of adult worldwide population; the same organization foresees that 438 million people worldwide will be suffering from this disease in 2030.
A study performed in United Kingdom, based on The Health Improvement Network (THIN) data, revealed that between 1996 and 2005 the prevalence of diabetes increased from 2.8% to 4.3% and incidence also increased from 2.7 per 1000 people-year to 4.42 per 1000 people-year [3].

In 2014, 9% of adults 18 years and older had diabetes. In 2012 diabetes was the direct cause of 1.5 million deaths. More than 80% of diabetes deaths occur in low- and middle-income countries [4]. According to data presented by World Health Organization (WHO), the prevalence of diabetes in 2000 was about 171,000,000 and it is estimated to be around 366,000,000 in 2030 [5].

Diabetes remains the leading cause of blindness and renal failure in U.S. and its total number of cases continues to increase. In addition, diabetes is associated with neuropathy, vascular disease leading to amputation, and markedly increases the risk of heart disease, birth defects and other serious problems. The WHO has predicted a worldwide epidemic of diabetes over the next 25 years that will strike even harder at less-developed countries as they become more westernized [2].

It is estimated that in 2014 there were 382 million people with diabetes and that in 2035 this value will increase to 592 million. The number of people with type 2 diabetes is increasing in all countries. The biggest portion of people with type 2 diabetes has ages comprised between 40 and 59 years of age. There are 179 million people with diabetes who do not know they have the disease. Diabetes led to 4.9 million deaths in 2014 [6].

In Portugal, in 2014 the estimated prevalence of Diabetes in population with ages between 20 and 79 years (7.8 million of individuals) was 13.1%, i.e. more than 1 million of Portuguese people in this age range had Diabetes. The impact of aging on the age structure of Portuguese population (20-79 years) was reflected in an increase of 1.4 percentage points of prevalence rate of Diabetes between 2009 and 2014, which corresponded to a growth of

about 12%. During the last decade, in Portugal, it has been observed a significant decrease in the number of potential years of life, lost by DM. Diabetes assumes a preponderant role in the causes of death, and it was the cause of 4.0% of deaths occurred in 2014 [6].

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces [4]. Diabetes is not a single disease, but is constituted by several complex disorders that share the major common features – elevated levels of glucose in the blood, abnormalities in lipid metabolism and increased risk for long-term micro- and macrovascular complications [2].

There are three main forms of diabetes, Gestational diabetes, Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus (T2DM). Despite a brief resume will be herein presented for the first two, the present work will focus on T2DM.

Gestational diabetes is hyperglycaemia with blood glucose values above normal but below those diagnostic of diabetes, occurring during pregnancy. Women with gestational diabetes are at an increased risk of complications during pregnancy and at delivery. They are also at increased risk of type 2 diabetes in the future [4].

Type 1 diabetes is characterized by deficient insulin production and requires daily administration of insulin. This condition is caused by a lesion in the β-cells of the pancreas. However, the trigger mechanism is not known and it is not preventable with current knowledge [4, 7].

The most common form of diabetes and the major cause of the worldwide epidemic of the disease is T2DM. This comprises 90% of people with diabetes around the world, and is largely the result of excess body weight and physical inactivity. It results from the body's ineffective use of insulin. The metabolic defects underlying T2DM are a triad of insulin resistance, β-cell dysfunction and impaired hepatic glucose production. It is driven primarily by insulin resistance, which can affect multiple tissues of the body and eventually lead to relative insulin deficiency. Insulin resistance is the pathophysiologic hallmark of this condition. The imbalance between energy supply and expenditure increases the concentration of fatty acids in the blood. This in turn reduces glucose utilization in muscle and fatty tissues. The result is a resistance to insulin, forcing an increase of insulin release. The resulting down-regulation of the receptors further raises insulin resistance. With insulin resistance, increased amounts of insulin may be required to achieve a given hypoglycaemic effect. Early in the natural history of T2DM, the pancreas may be able to produce this increased insulin quantity, and many people with this condition become hyperinsulinemic. Initially, the hyperinsulinemia may be able to compensate for the insulin resistance. Over the time, the numbers of β-cells often decline, and hyperinsulinemia may be insufficient to overcome the insulin resistance, and clinical diabetes may be diagnosed [2, 4, 7-9].
Until recently, this type of diabetes was seen only in adults. However, the number of T2DM cases is rising in children and young adults, mostly due to lifestyles changing [2, 4]. This condition appears to have a strong genetic component and it is found more frequently in certain families and ethnic minority groups, such as Hispanics, African-Americans, Pacific Islanders and American Indians [9]. Since the risk of long-term complications of diabetes increases with duration of the disease, as more and more individuals develop diabetes at younger and younger ages, the medical community will be faced with a rapidly growing

population of individuals at risk for the eye, kidney, vascular, and neurologic complications of diabetes [2, 4].

II. Current therapeutic options of diabetes

The treatment of diabetes has come a long way in the last century. Starting with the discovery of insulin in 1921, it has seen also the development of antidiabetic drugs [2].

The development of oral drugs to treat T2DM has been one of the major milestones in the modern era of diabetes treatment. Since the 1950s, it has been possible to treat T2DM with tablets. In recent years, newer drugs have become available, targeting specific components of the spectrum of pathophysiologic abnormalities, regulating glucose input, and also addressing glucose utilization and disposal through impacts on insulin resistance and insulin deficiency [1, 2].
The following table (Table 1) presents the currently-available glucose lowering agents grouped by their chemical class [1, 2, 10, 11]:

Table 1 - Currently-available glucose lowering agents

Class	Cellular Mechanism	Primary Action(s)	Example of Compound(s)
Biguanides	Activates AMP-kinase	Decrease hepatic glucose production	Metformin
Sulfonylureas (2nd generation)	Closes K_{ATP} channels on β-cell plasma membranes	Increase insulin secretion	Glyburide/ glibenclamide Glipizide Gliclazide Glimepiride
Meglitinides	Closes K_{ATP} channels on β-cell plasma membranes	Increase insulin secretion	Repaglinide Nateglinide
Thiazolidinediones or Glitazones	Activates the nuclear transcription factor PPAR-γ	Increase insulin sensitivity	Pioglitazone Rosiglitazone
α-Glucosidase inhibitors	Inhibits intestinal α-glucosidase	Slows intestinal carbohydrate digestion/absorption	Acarbose Miglitol Voglibose
DPP-4 inhibitors	Inhibits Dipeptidyl-Peptidase 4 (DDP-4) activity, increasing postprandial active incretin (Glucagon-Like Peptide-1 [GLP-1], glucose-dependent insulinotropic polypeptide [GIP]) concentrations	Increase insulin secretion (insulin-dependent) Decrease glucagon secretion (glucose-dependent)	Sitagliptin Vildagliptin Saxagliptin Linagliptin Alogliptin
Bile acid sequestrants	Binds intestinal bile acids, increasing bile acid production	Unknown, probably decrease hepatic glucose production and increase incretin levels	Colesevelam

Insulins	Activates insulin receptors	Increase insulin disposal Decrease hepatic glucose production	Human NPH Human regular Lispro Aspart Glulisine Glargine Detemir Premixed
Sodium glucose co-transporters 2 (SGLT2) inhibitors	Inhibit glucose re-absorption in the proximal renal tubules	Increase urinary glucose excretion Reduce glucose levels in blood	Canagliflozin Dapagliflozin Empagliflozin

III. Incretin effect

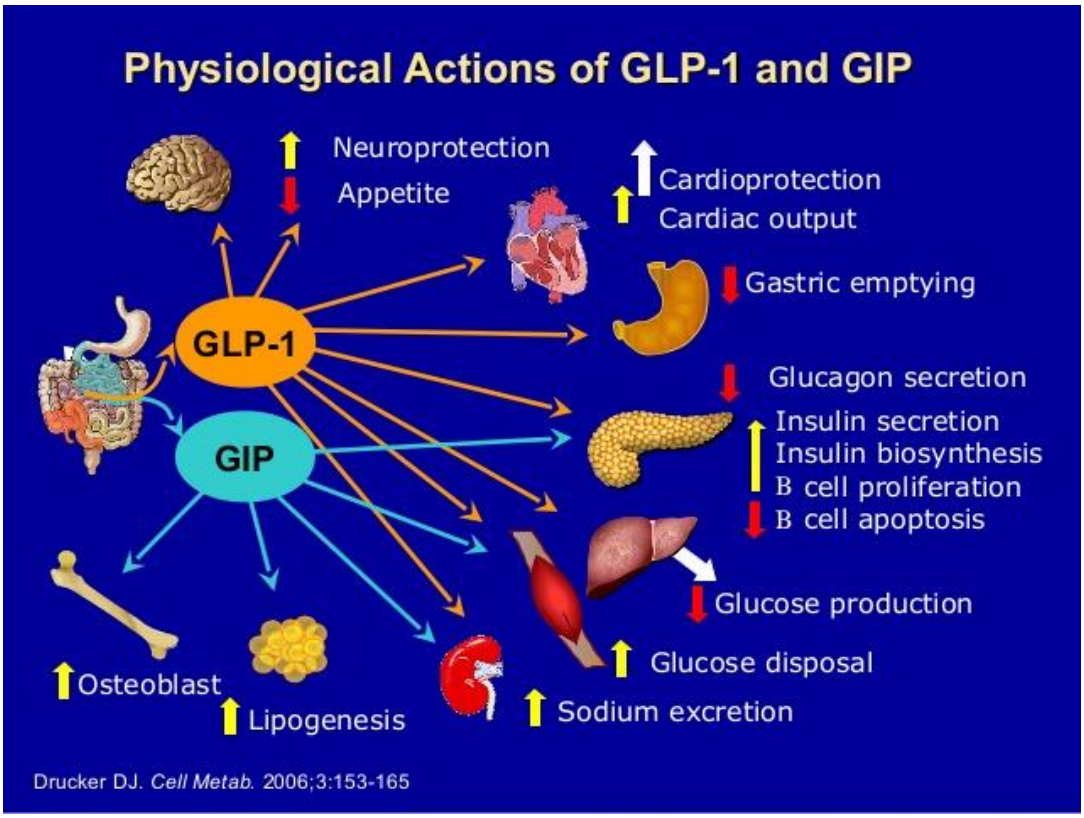

Figure 1 – Physiological Actions of Incretins. In Dr. sherif W. Mansour Entero Insular Axis *(http://www.slideshare.net/drsherif36/entero-insular-axis-dr-sherif-w-mansour).*

The existence of the incretin system has been known for a number of years, but it was not until recently that this knowledge has translated into a mode of treating diabetes, since incretin effect is significantly reduced or absent in people with T2DM. It had been observed for many years that when glucose was taken orally, the resulting insulin stimulatory response was greater than when glucose was given intravenously. This difference in response is referred to as the *Incretin Effect*. In other words, the *Incretin Effect* designates the

amplification of insulin secretion elicited by hormones from the gastrointestinal (GI) tract. It is primarily due to the effects of two hormones secreted from cells in the small intestine when food enters the stomach and which stimulate insulin secretion and glucagon suppression, **glucagon-like peptide-1 (GLP-1)** and **glucose-dependent insulinotropic polypeptide (GIP)** (Figure 1). After secreted by the GI tract during food intake, the incretin hormones link to the pancreatic β-cell receptor, stimulating insulin secretion in response to glucose absorption. As GLP-1 and GIP stimulate insulin secretion through a glucose-dependent mechanism, insulin is only secreted when hyperglycaemia is verified [2, 3, 7, 12-14]. Beyond this effect in pancreas, incretins have also effects in several other organs, for instance heart, kidney, liver and brain (Figure 1).

GLP-1, a 30 amino acids peptide, is the most important incretin and its modulation has proven being useful in T2DM therapy. It is secreted by the L-cells in the distal small intestine (jejunum and ileum) upon stimulation by the presence of incoming nutrients. GLP-1 is rapidly metabolized by the enzyme Dipeptidyl-Peptidase 4 (DPP-4), an enzyme linked to cell membranes which is presented in several tissues, such as liver, kidneys, bowel, endothelial cells and lymphocytes, and others. Thus, GLP-1 half-life is about 4-5 minutes (Figure 2) [1, 2, 15].

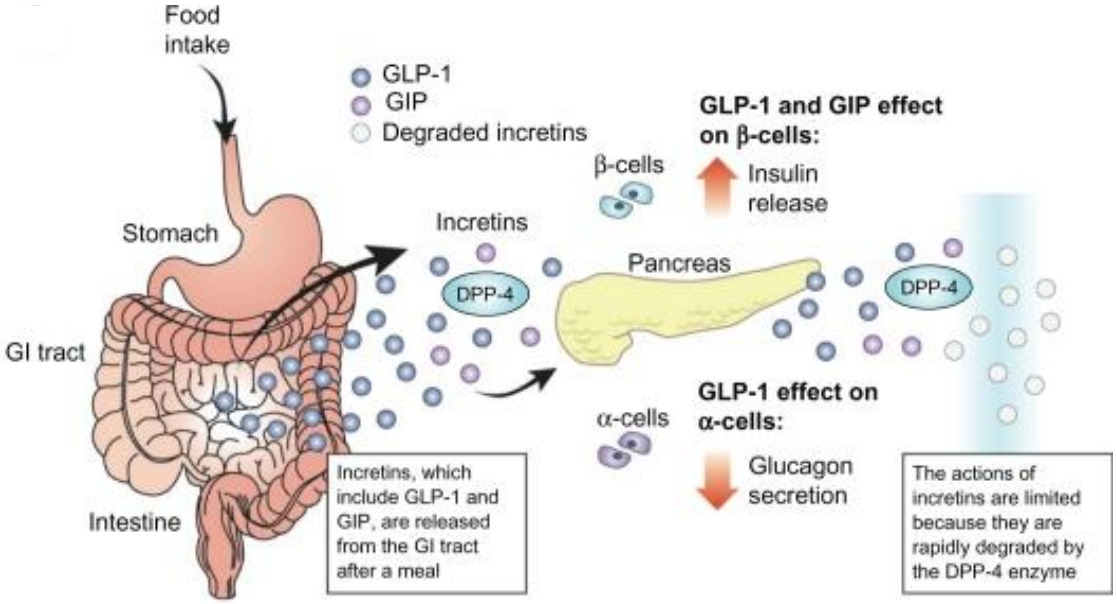

Figure 2 – Action of DPP-4 enzyme on GLP-1. In Kirsten Kulasa et al., 2010 [16].

III. 1. GLP-1 Receptor Agonists

i. Pharmacology and distribution of the GLP-1R

G protein-coupled receptors (GPCRs) constitute a large family of receptors that sense molecules outside the cell and activate inside signal transduction pathways and cellular responses [17].

Most of the effects of GLP-1, such as improvement of glycaemic control, are mediated by direct interaction with GLP-1R on specific tissues, for instance in pancreas the increasing insulin release and decreasing glucagon release, in the brain the decreasing appetite and in the stomach the delayed gastric emptying and decreasing appetite as well (Figure 1). However, the actions of GLP-1 in liver, fat, and muscle most likely occur through indirect mechanisms. GLP1 receptor activation directly promotes cell proliferation and enhances cell survival in several tissues including β-cells, neurons, fibroblasts, cardiomyocytes and thyroid C-cells [1, 12, 14, 15, 17-20].

i. Mode of action of GLP1R – mediated antidiabetic effects

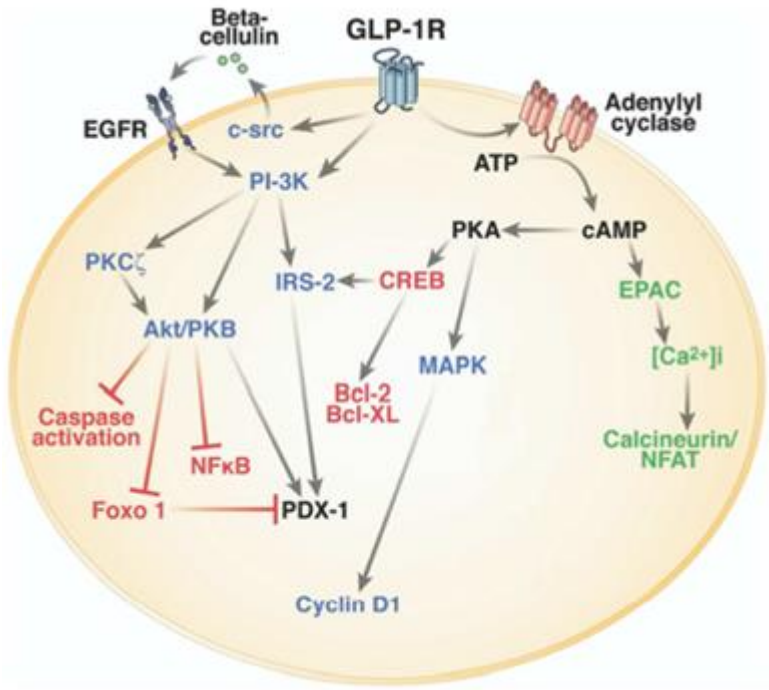

Figure 3 - Intracellular signaling pathways of GLP-1R in the pancreatic β-cell. ***Adapated from Véronique Gigoux et al., 2013 [17]***

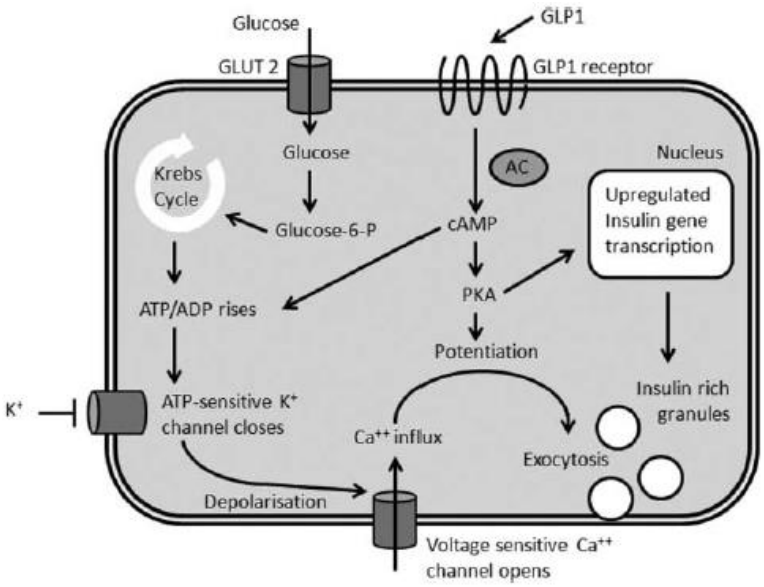

Figure 4 - Pancreatic β-cell - stimulation of insulin secretion and biosynthesis. ***In Roman Vangoitsenhoven et al., 2012 [15].***

One of the main physiological roles of GLP-1 is to enhance insulin secretion in a glucose-dependent manner. To stimulate insulin secretion and biosynthesis (Figure 3, green), GLP1 binds to its specific GPCR, GLP-1R, activating downstream pathway of adenylate cyclase, which elevates intracellular cAMP levels leading to activation of Protein Kinase A (PKA) and cAMP-regulated guanine-nucleotide exchange factor II (cAMP-GEFII, also known as Epac2) signaling pathways. In the β-cell (Figure 4), GLP-1R activation accelerates glycolytic and mitochondrial metabolism of glucose, which is incorporated into the cell through GLUT-2, while also rendering K^+-ATP channels more sensitive to the increase of ATP/ADP concentration ratio generated by the intracellular metabolism of glucose. In the presence of stimulatory levels of glucose and GLP-1, Ca^{2+} influx through the Ca^{2+} channels feeds forward into mobilization of Ca^{2+} from intracellular stores by Ca^{2+}-induced Ca^{2+} release through PKA and cAMP-GEFII-dependent mechanisms. Ca^{2+} mobilization from intracellular stores will stimulate mitochondrial ATP synthesis, which will promote further membrane depolarization via closure of K^+-ATP channels. ATP is also required for stimulation of exocytosis of the insulin-containing granules. The elevation in the cytoplasmic free Ca^{2+} concentration triggers the exocytotic response that is further potentiated by increased cAMP levels. This effect is mostly attributable to the ability of cAMP to accelerate granule mobilization resulting in an increased size of the pools of granules that are immediately available for release. These effects depend both on cAMP binding to PKA and cAMP-GEFII. These channels are sensitive to the intracellular ATP levels and, thereby, to glucose metabolism of the β-cells, but may also be affected (closed, resulting in subsequent depolarization of the plasma membrane and opening of voltage-sensitive Ca^{2+} channels) by PKA activated by GLP-1. In other words, GLP-1 increases glucose-induced membrane depolarization and therefore enhances insulin secretion in a glucose-dependent manner [1, 7, 14, 15, 17, 18, 20].

GLP-1 plays also a key role in the homeostasis of β -cell mass by inducing β -cell proliferation (Figure 3, in blue) and protecting against apoptosis which favour an expansion of β -cell mass (Figure 3, in red). When GLP-1 binds to its receptor it induces homeobox-1

gene activation, which promotes in the periductal pancreatic cells the differentiation towards β-cells, inhibiting the apoptosis. These functions are mediated via the activation of the cAMP/PKA/CREB (cAMP-responsive element binding protein) and the transactivation of the epidermal growth factor receptor (EGF-R) leading to the activation of phosphatidylinositol-3 kinase (PI3K), Protein Kinase Cζ (PKCζ), Akt-protein kinase B, Extracellular Regulated Kinase (ERK1/2, also named Mitogen-Activated Protein Kinase [MAPK]) signaling pathways and to the up-regulation of the expression of the cell cycle regulator cyclin D1. The antiapoptotic effect of GLP-1 in β-cells also involves β-arrestin1 recruitment by GLP-1R which mediates the ERK1/2 activation leading to the phosphorylation and inactivation of the pro-apoptotic protein Bad [17].

In addition to its stimulatory effect on insulin secretion, in the α-cell, GLP-1R activation inhibits glucagon secretion. In combination with enhanced insulin secretion, this decrease of glucagon leads to an improvement of glucose homeostasis, in particular in patients with T2DM [15, 17].

III. 2. Approved medicines of GLP-1R agonist class

The GLP-1R agonists mimic the GLP-1 function in order to enhance insulin secretion after food-intake, restoring the incretin function, while are protected from the DPP-4 deactivation. This is achieved by binding to a GLP-1R that resides in the β-cell [1, 2, 15].

The first GLP-1R agonist to reach the market was exenatide, under the trade name BYETTA, which was approved in November 2006 in the EU and April 2005 in the U.S. It was discovered when it was noted that salivary protein from the *Gila monster* had properties similar to GLP-1. A synthetic version of this substance was produced and tested, and found to be effective. It has greater than 50% structural overlap with human GLP-1, binds to the human GLP-1R on the β-cell and is resistant to DPP-4 degradation [2].

Following BYETTA several other medicinal products, belonging to GLP-1R agonists' family, were approved. The following tables (Table 2 and Table 3) present the approved agonists of the GLP-1R in EU and U.S., respectively.

Table 2 - GLP-1R agonists approved in EU

Medicinal Product	Active substance	Authorisation date	Marketing Authorisation Holder	Strength	Pharmaceutical Form
BYETTA	Exenatide	November 2006	AstraZeneca AB	5 micrograms (mcg) 10 mcg	Solution for injection
VICTOZA	Liraglutide	June 2009	Novo Nordisk A/S	6 mg/ml	Solution for injection in pre-filled pen

BYDUREON	Exenatide extended-release	June 2011	AstraZeneca AB	2 mg	Powder and solvent for prolonged release suspension for injection
LYXUMIA	Lixisenatide	February 2013	Sanofi-Aventis Groupe	10 mcg 20 mcg 10 mcg + 20 mcg	Solution for injection
EPERZAN	Albiglutide	March 2014	GlaxoSmithKline Trading Services Limited	30 mg 50 mg	Powder and solvent for solution for injection
TRULICITY	Dulaglutide	November 2014	Eli Lilly Nederland B.V.	0.75 mg 1.5 mg	Solution for injection

Table 3 - GLP-1R agonists approved in U.S.

Medicinal Product	Active substance	US authorisation date	Marketing Authorisation Holder	Strength	Pharmaceutical Form
BYETTA	Exenatide	April 2005 October 2009	AstraZeneca AB AMYLIN	250 mcg/ ml	Solution for injection
VICTOZA	Liraglutide	January 2010	Novo Nordisk Inc	6 mg/ml	Solution for injection in pre-filled pen
BYDUREON	Exenatide extended-release	January 2012	AstraZeneca AB	2 mg	Powder and solvent for prolonged release suspension for injection
ADLYXIN	Lixisenatide	July 2016	Sanofi-Aventis US	0.05 mg/ml 0.1 mg/ml	Solution for injection
TANZEUM	Albiglutide	April 2014	GlaxoSmithKline LLC	30 mg	Powder and solvent for solution for injection
TRULICITY	Dulaglutide	September 2014	Eli Lilly and Co	0.75 mg/ 0.5 ml 1.5 mg/ 0.5 ml	Solution for injection

These medicinal products have slight different therapeutic indications, as stated in the following table (Table 4).

Table 4 - Approved therapeutic indications

MEDICINAL PRODUCT	THERAPEUTIC INDICATIONS
BYETTA	For treatment of T2DM in combination with: • metformin, • sulphonylureas (SUs), • thiazolidinediones (TZDs), • metformin and a SU, • metformin and a TZD in adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies. As adjunctive therapy to basal insulin with or without metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these agents [21, 22].
BYUDUREON	For treatment of T2DM in combination with: • metformin, • SUs, • TZDs, • metformin and a SU, • metformin and a TZD in adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies [23].
VICTOZA	Treatment of adults with T2DM to achieve glycaemic control: • monotherapy, when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance or contraindications; and as combination therapy, • combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control [24].
LYXUMIA/ADLYXIN	Treatment of adults with T2DM to achieve glycaemic control in combination: • with oral glucose-lowering medicinal products • and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control [25-27].
EPERZAN/TANZEUM	Treatment of T2DM in adults to improve glycaemic control: • monotherapy, when diet and exercise alone do not provide adequate glycaemic control in patients for whom use metformin is considered inappropriate due to contraindications or intolerance; • add-on combination therapy, in combination with other glucose-lowering medicinal products including basal insulin, when these, together with diet and exercise, do not provide adequate glycaemic control. [28, 29]
TRULICITY	In adults with T2DM to improve glycaemic control: • monotherapy, when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of

	metformin is considered inappropriate due to intolerance or contraindications; • add-on therapy, in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control [30, 31].

The present work will focus on the GLP-1R agonists therapeutic class which includes five active substances and six different medicinal products approved both in the EU and in the U.S. (please refer to the tables above for further details).

Lixisenatide and albiglutide have different trade names in the EU and in the U.S.. Therefore, whenever these active substances are analysed, both trade names will be referred.

THESIS OBJECTIVES

Despite GLP-1R agonists are authorised in Europe since 2006 (BYETTA's approval year), in Portugal only in 2014 the first GLP-1R agonists were reimbursed. The reimbursement was approved for VICTOZA in January 2014 and for BYDUREON in October 2014. BYETTA's reimbursement request was rejected not showing therapeutic nor economic advantage. In coming years, it is expected that several other GLP-1R agonists become reimbursed.

Reimbursement will allow much more patients to have access to these medicines, which in turn will increase the data not only on these medicinal products' benefits but also on their adverse effects profile.

The post-marketing experience gathered by other countries, both in the Europe and in the U.S., is of most importance, as it enables to draw a more accurate safety profile for these medicines and it allows deducing which will be the most serious adverse reactions to be expected in Portuguese patients.

Therefore, the main goals of the present work are drawing a safety profile for GLP-1R agonists and conclude on the need and/or opportunity of adapting their RMPs for the new markets, taking into account the safety data collected both in the EU and in the U.S..

METHODOLOGY

I. Research sources

EMA and FDA were contacted by email, in order to obtain more and the most recent safety data regarding the medicinal products herein evaluated. EMA provided the RMPs for the concerned medicines and they indicated that the European Public Assessment Reports (EPARs) are available in the EMA's website. Regarding FDA, they communicated that all data available are published in their website.

Therefore, the data collected, reviewed, analysed, compared and summarised has been obtained mainly through online research in the following sources:

Table 5 - Data sources used

Data sources	Analysed information
Pubmed website [32] The New England Journal of Medicine website [33] Books, magazines, reports and presentations	Articles, reviews and data on: - Diabetes epidemiology and physiopathology - Mechanism of action of the GLP-1R agonists - Safety profile of GLP-1R agonists
EMA's website [34]	- EPARs - Summaries of the Product Characteristics (SmPCs) - Current approved antidiabetic therapies
FDA's website [35]	- Risk Evaluation and Mitigation Strategy (REMS) - Medical review - Summary review - Risk assessment and risk mitigation review(s) - Approved information
European database of suspected adverse drug reaction reports website [36] (database created in 2012)	Suspected adverse drug reactions, occurred in the EU and non-EU, reported to EudraVigilance.
DrugCite.com website [37]	Adverse Events (AEs) reported through the FDA Adverse Events Reporting System (FAERS), up to the third quarter of 2012
Risk Management Plans (RMPs) [9, 11, 38-41]	- Safety concerns identified to each medicinal product - Routine and additional pharmacovigilance activities implemented

For AEs listing, Medical Dictionary for Regulatory Activities (MedDRA 19.0) was used.

II. Data treatment

In a first step, a comparison in a table format between EPARs (nonclinical and clinical data) and RMPs is presented for each medicinal product. Following this, it is presented a resume table identifying the risks considered by EMA and those ones accepted by FDA.

Since BYETTA and BYDUREON contain the same active substance, only the pharmaceutical form is different, it seems important to assess them in a stricter manner

allowing to understand if the extended-release formulation has a relevant role in the expression of any adverse reaction.

In a second step, a comparison of adverse reactions reported both in the EU and in the U.S., if possible, within each medicinal product is presented. The methodology hereinafter described is similar to the one used by Francisca Lemos in her master thesis [42]. The data collected and compared was made available through different databases, with different data sources formats and classifications (Table 6).

Table 6 - Differences in presentation of data pertaining to Adverse Drug Reactions (ADRs) reported in the EU and in the U.S.

Data characteristics	EU database of suspected adverse drug reaction reports [36]	DrugCite.com website [37]
Source	**EudraVigilance** - Comprises reports from national competent authorities and pharmaceutical companies that hold marketing authorisations for the medicines.	**FAERS** - Includes AEs if the drug is flagged as a suspect drug causing the AE.
Updating frequency	**Cases reported up to the end of the previous month** (updates are done on the 15th of the month)	Uncertain (information not available) - At the time of data collection, only had data from Q1 2004 **until Q3 2012**
Data format	Chart format	Chart format
Charts data labels available	Only displayed in the online format (for the purpose of this project, those were retrieved one by one)	Yes
Charts data classifications	Number of **individual cases by reaction groups** – MedDRA System Organ Class (SOC) The reaction groups are based on a classification of the side effect (also known as adverse drug reaction), using the MedDRA dictionary of terms	Top **categories of AEs** – MedDRA High-Level Group Terms (HLGT)

Since the data retrieved from both the EU and the U.S. databases was significantly different, some treatment of data was necessary for enabling the comparison of the EU and the U.S. data.

For each GLP-1R agonist, it was firstly analysed the EU and U.S. raw data and only then, a cumulative data chart was created. For that cumulative data chart to be created, some treatment of data was performed:

- U.S. data classification was re-arranged and grouped into a classification similar to EU data classification: MedDRA SOC

- Only MedDRA SOC totals were displayed in the cumulative chart. Comparative charts, whenever possible, will be presented containing the EU and the U.S. data side-by-side.

Regarding the ADRs data, all SOCs were assessed and only the relevant ones for the present work have been analysed. The most prevalent ADR terms were grouped into their respective PT term. The obtained results from both databases of the EU and the U.S., whenever possible, are presented in chart.

RESULTS

BYETTA

BYETTA 5 mcg solution for injection is a parenteral drug product for subcutaneous (SC) administration, twice a day (BID). It contains exenatide as active substance, which is an incretin mimetic. Exenatide was originally isolated from the salivary secretions of *Heloderma suspectum* (Gila monster), in which it circulates after meal initiation and may have endocrine functions [43].

Exenatide is a chemically synthesized 39-amino-acid peptide. The synthesis using protected L-amino acids has been stereochemically controlled [43].

The amino acid sequence of exenatide partially overlaps (53%) that of human GLP-1. Exenatide has been shown to bind to and activate the known human GLP-1R *in vitro* [22, 38].

These medicinal product is approved in several therapeutic combinations, as identified in Table 4 - Approved therapeutic indications.

Regarding the BYETTA' safety profile, comparative analyses are presented. A comparison between safety information included in EPAR (nonclinical and clinical data) and in RMP is presented in Table 7. Table 8 resumes the safety concerns considered by EMA and those ones accepted by FDA.

Table 7 - Comparative analysis on BYETTA' safety profile

	Nonclinical data [43]	Clinical data [43]	RMP data[38]
Safety concerns	Rat: - Acute administration did not affect thyroid hormones T3 and T4 - Reduction of plasma levels of thyroid stimulating hormone - Increased incidence of benign thyroid C-cell adenomas (highest dose - 130 times human exposure) **Carcinogenicity** Rat: - Increased incidence of benign thyroid C-cell adenomas (female; highest dose) - No increased incidence in C-cell carcinomas **Reproduction Toxicity** Mice / Rabbit: - Maternal food consumption and body weight reduced - Foetal growth slowed and skeletal variations – changes in rib pairs or vertebral ossification sites and wavy ribs - Maternal toxicity.	**Potential risks** - Anti-exenatide antibodies; - Cardiovascular (CV) Events; - Risks of Elevated Pulse Rate; - Malignant Neoplasms; - Dehydration and Acute Renal Impairment; - Pancreatitis; - Increased International Normalisation Ratio (INR) with concomitant warfarin. **Information to be completed** - Adolescents; - Pregnant women; - Very elderly (>= 75 years of age).	**Identified risks** At this time, no risks have been identified that would require further systematic study. **Potential risks** - Anti-exenatide Antibodies - CV Events - Malignant Neoplasms - Dehydration and acute renal impairment - Pancreatitis - Increased INR with concomitant Warfarin **Missing information** - Adolescents - Pregnant women - Very elderly (>= 75 years of age)

Table 8 - Summary of safety concerns considered by EMA and FDA

	EMA [38, 43]	FDA [44]
Safety concerns	**Identified risks** No risks have been identified that would require further systematic study. **Potential risks** - Anti-exenatide Antibodies - CV Events - Malignant Neoplasms - Dehydration and acute renal impairment - Pancreatitis - Increased INR with concomitant Warfarin **Missing information** - Adolescents - Pregnant women - Very elderly (>= 75 years of age)	- GI side effects: nausea, vomiting, diarrhoea and dyspepsia - Decrease the absorption of concomitant oral drugs - Hypoglycaemia, when used together with a SU - Anti-exenatide antibodies/ Immunogenicity - Use during pregnancy

The safety concerns identified throughout the investigational cycle were presented in the aforementioned tables. Nevertheless, it is well-known that the results acquired during the clinical trials are scarce, when comparing to the "real world" data. Therefore, the post-marketing data, i.e. the ADRs reported in the EU and in the U.S., are presented in individual charts. Additionally, a comparison of adverse reactions reported both in the EU and in the U.S., grouped by SOC, can be seen in a single chart.

- European database of suspected adverse drug reaction reports

The data herein presented was retrieved from European database adrreports.eu [36]. This website gives access to web reports on suspected ADRs by medicine or by active substance name. All the data displayed in the web reports is taken from EudraVigilance, a system designed for collecting reports of ADRs occurred within and outside the European Economic Area (EEA) [36]. This includes reports received from healthcare professionals and patients, reported by national competent authorities and Marketing Authorisation Holders (MAHs).

The following charts (Chart 1 and Chart 2) illustrate the number of the ADRs reported up to July 2016 to EudraVigilance, grouped by SOC and by PT, respectively.

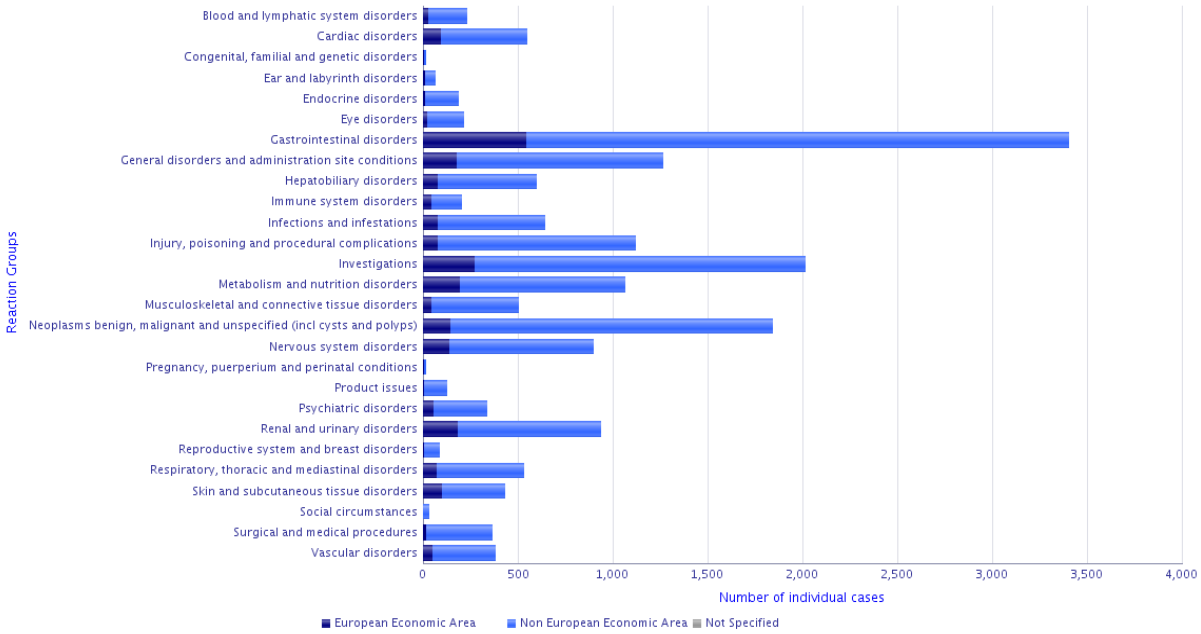

Chart 1 - Number of Individual Cases by Reaction Groups sorted by Geographic Origin in the EU for BYETTA

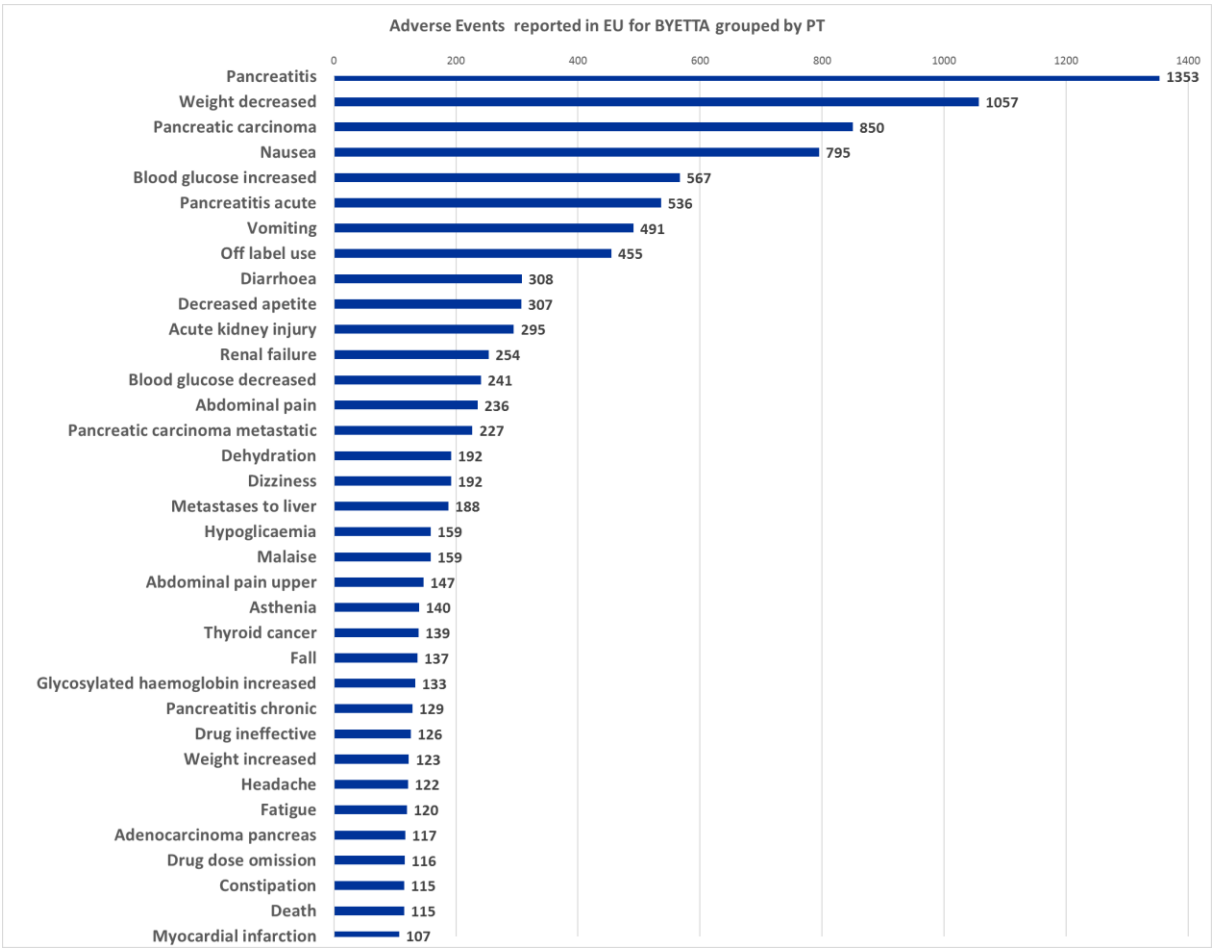

Chart 2 - Adverse Events reported in the EU for BYETTA grouped by PT

- **FDA Adverse Events Reporting System (FAERS) Data (DrugCite.com)**

The data herein presented was made available by DrugCite database [37]. The results included reports submitted by physicians, healthcare consumers, lawyers amongst others, previously assessed by FDA scientific staff.

The following charts (Chart 3 and Chart 4) illustrate the number of the ADRs reported up to the Q3 2012 to FDA, grouped by SOC and by PT, respectively.

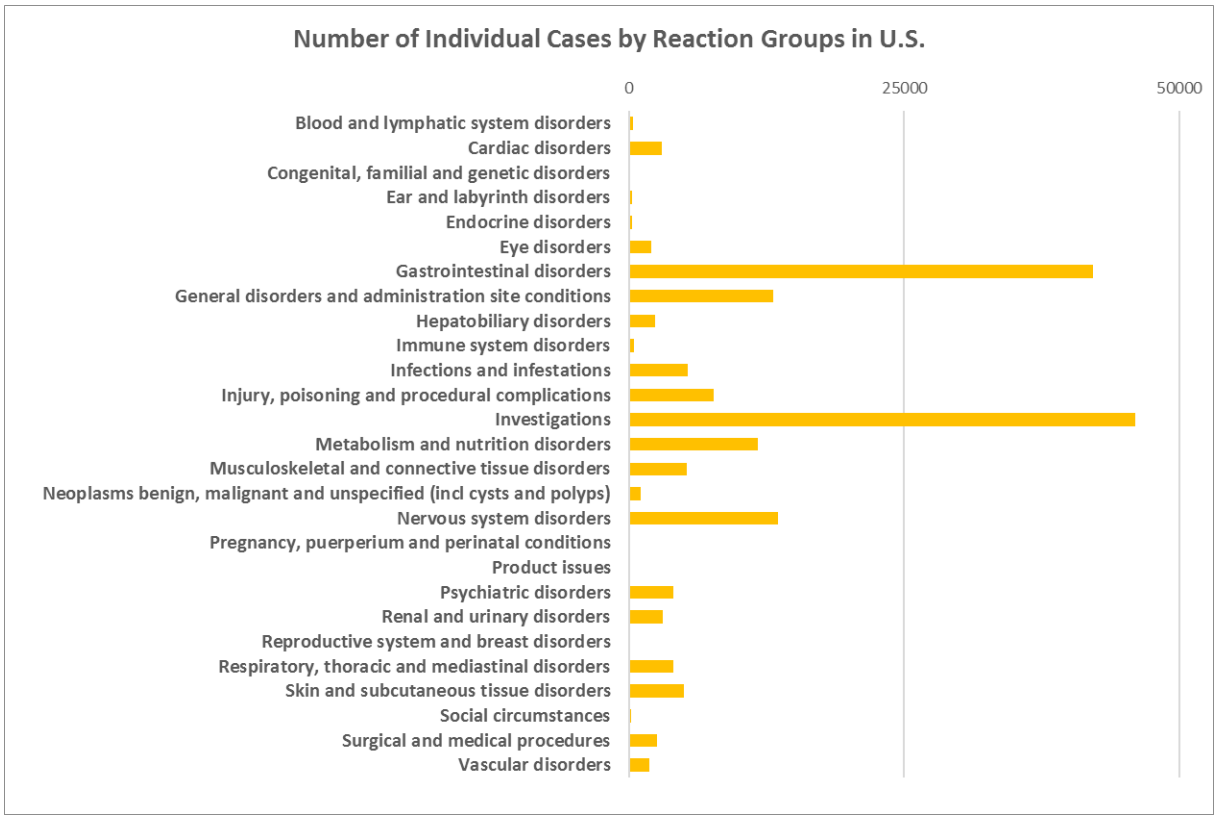

Chart 3 - Number of Individual Cases by Reaction Groups in the U.S. for BYETTA

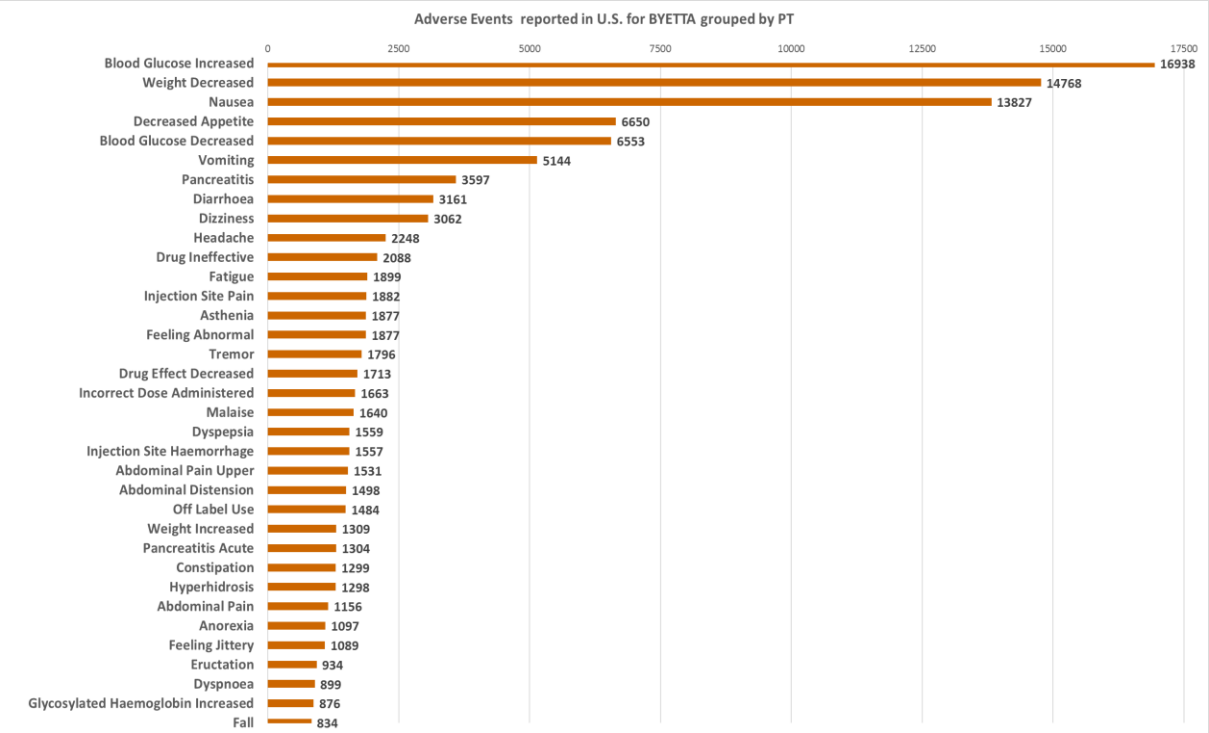

Chart 4 - Adverse Events reported in the U.S. for BYETTA grouped by PT

- **Comparison of adverse events reported in EU and U.S., grouped by SOC**

Herein it is included a cumulative chart regarding the ADRs reported for BYETTA both in the EU and in the U.S. grouped by SOC. This comparison allows a visually enhanced perception of differences between the EU (blue) and the U.S. (yellow) data.

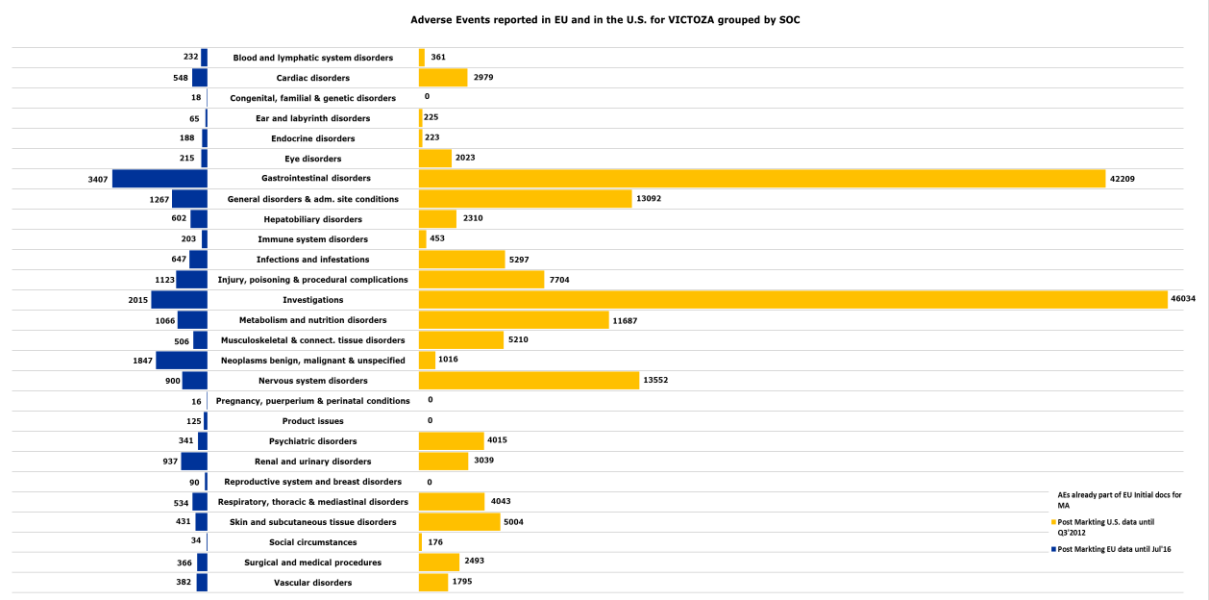

Chart 5 - Adverse Events reported in the EU and in the U.S. for BYETTA grouped by SOC

Following the analysis of the charts and tables previously presented, it became clear that there were some similarities and some discrepancies between the EU and the U.S. data:

Main similarities:

- *GI disorder SOC* is the most and the 2nd most prevalent in the EU and in U.S., respectively. Therefore, GI events, such as nausea, vomiting and diarrhoea, are among the ones most reported in both geographical areas.
- Pancreatitis belong to the most reported ADRs.
- *Cardiac disorders SOC* is amongst the less prevalent.
- Weight decreased is the second most reported ADR.
- Blood glucose increased belongs to the top 5 of the most reported ADRs, having the first place in the U.S..
- Anti-exenatide antibodies/immunogenicity (such as anaphylactic reactions), were identified as a risk in the EU an in the U.S.. Nevertheless, they were not reflected in the post-marketing reports, not being frequently reported.

Main discrepancies:

- GI AEs and hypoglycaemia were identified as a risk in the U.S. but not in the EU.
- Pancreatitis, cardiovascular events and renal impairment were considered potential risks in the EU but not in the U.S.
- Renal conditions and hypoglycaemia remain amongst the 35 most reported ADRs in the EU but not in the U.S..
- Malignant neoplasms were, during the pre-marketing phase, considered potential risks in the EU but not in the U.S.. Accordingly, the *Neoplasms benign, malignant and unspecified SOC* is the third most reported in EU, but in the U.S. this SOC is comprised under the ones less reported.
- *Nervous system disorders* is the 3rd most prevalent SOC in the U.S., but not in the EU.
- The visual perception enabled by Chart 5 lead to hypothesised that in the U.S. the reporting rate is much higher than in the EU. Therefore, the real proportion of results is not comparable. However, if a dispersion curve is imagined, it is possible to realize that the trend could be similar when the same number of U.S. reports will be achieved in the EU.

BYDUREON

BYDUREON 2 mg powder and solvent for prolonged-release suspension for injection is a parenteral drug product for weekly (QW) and SC administration of the known active substance exenatide. Exenatide QW consists of exenatide (5%) and sucrose (2%) encapsulated within biodegradable poly(D,L-lactide-co-glycolide) (PLG) microspheres that are designed to release exenatide over an extended period of time [45].

BYDUREON thereby represents the first long acting GLP-1 analogue submitted for marketing authorisation. In Exenatide QW, exenatide will remain in plasma at levels above lower limit of quantification (LLOQ) (10 pg/ml) for 10 weeks after treatment interruption [45].

In comparison with Exenatide BID, overall systemic exposure is higher following treatment with BYDUREON and the washout period is longer, which can have potential implications for clinical safety [45].

This medicinal product is approved in several therapeutic combinations, as identified in Table 4 - Approved therapeutic indications.

The primary pharmacologic, pharmacokinetic, and toxicological properties of the exenatide peptide were well characterised during the development of Exenatide BID. Therefore, most of the nonclinical pharmacology information presented for BYDUREON stems directly from the nonclinical program for Exenatide BID. The primary aim of the nonclinical studies conducted specifically for exenatide QW focused on determining the impact of the extended-release formulation on the pharmacologic, pharmacokinetic, and toxicological profile of exenatide. In addition, these studies assessed the local tolerance (i.e. injection site reaction) of the exenatide QW formulation and also monitored for the emergence of anti-exenatide antibodies [45, 46].

Studies with exenatide QW were performed to compare pharmacokinetic profiles between the two formulations. After a SC injection of exenatide QW, absorption occurs over an extended period of time, i.e. weeks in monkeys and rats [45].

The following tables (Table 9 and Table 10) encompass the comparative analyses regarding the safety profile of BYDUREON, either between information included in EPAR and in RMP as well as between the safety concerns accepted by EMA and by FDA.

Table 9 - Comparative analysis on BYDUREON' safety profile

	Nonclinical data [45]	Clinical data [45]	RMP data [9]
Safety concerns	**Toxicokinetics** Rat/monkey: - Injection site reactions - Anti-exenatide antibodies **Carcinogenicity** Mice: - No increase in neoplastic lesions Rat: - Thyroid tumours (both sexes) – not of C-cell origin - Parathyroid gland adenoma (mid- and high-dose males) **Reproduction/ Developmental Toxicity** Rat: - Maternal and foetal toxicity (decreased food intake and body weight decrease; growth retardation/ developmental delay, respectively) **Local tolerance** - Injection site reactions **Antigenicity/ Immunogenicity** - Exenatide QW more immunogenic than for exenatide BID. Rat/ Monkey: - Antibodies observed	**Safety concerns** - Pancreatitis - Acute Renal Failure - Rapid Weight Loss - Risks associated with Anti-exenatide antibodies: focus on anaphylactic-type reactions – immunological events - Injection site related-events; hypersensitivity - Cardiac Events - Malignant Neoplasms: focus on pancreatic cancer and thyroid neoplasms - Adolescents – assess safety and efficacy - Pregnant Women – pregnancy registry - Very Elderly (≥ 75 years of age) - Use of exenatide in combination with TZDs - Severe GI Disease - Various Degrees of Impaired Renal - Hepatic Impairment	**Important identified risks** - Pancreatitis - Acute Renal failure - Rapid Weight Loss **Important Potential Risks** - Risk(s) associated with Anti-Exenatide Antibodies: focus on anaphylactic-type reactions - Cardiac events - Malignant Neoplasms: Focus on Pancreatic Cancer and Thyroid Neoplasms **Missing information** - Adolescents - Pregnant women - Very elderly (≥ 75 years old) - Potential for Concomitant use with TZDs - Severe GI disease - Various degrees of impaired renal function - Hepatic impairment

Table 10 - Summary of safety concerns considered by EMA and FDA for BYDUREON

	EMA	FDA [46]
Safety concerns	**Important Identified Risks** - Pancreatitis - Acute Renal failure - Rapid Weight Loss **Important Potential Risks** - Risk(s) associated with Anti-Exenatide Antibodies: focus on anaphylactic-type reactions - Cardiac events - Malignant Neoplasms: Focus on Pancreatic Cancer and Thyroid Neoplasms **Missing Information** - Adolescents - Pregnant women - Very elderly (≥ 75 years old) - Potential for Concomitant use with TZDs - Severe GI disease - Various degrees of impaired renal function - Hepatic impairment	- GI AEs (less frequently with BYDUREON than with BYETTA) - Renal impairment - Pancreatitis - Thyroid tumours: increased risk - Injection site nodules and reactions - CV: small increase in heart rate - Hypersensitivity/ immunogenicity (anti-exenatide antibodies) - Hypoglycaemia (in combination with SU)

All identified and potential risks discussed were initially identified in the clinical development program for exenatide BID or through post-marketing experience with Exenatide twice daily [45].

Despite BYETTA and BYDUREON contain the same active substance, the pharmaceutical form is different and it seems important to assess them distinctly. Therefore, the ADRs reported in the EU and in the U.S., are presented in individual charts. Additionally, a comparison of ADRs reported both in the EU and in the U.S., grouped by SOC, can be seen in a single chart.

- **European database of suspected adverse drug reaction reports**

The data herein presented was retrieved from European database adrreports.eu [36]. This website gives access to web reports on suspected ADRs by medicine or by active substance name. All the data displayed in the web reports is taken from EudraVigilance, a system designed for collecting reports of ADRs occurred within and outside the EEA [36]. This includes reports received from healthcare professionals and patients, reported by national competent authorities and MAHs.

The following charts (Chart 6 and Chart 7) illustrate the number of the ADRs reported up to July 2016 to EudraVigilance, grouped by SOC and by PT, respectively.

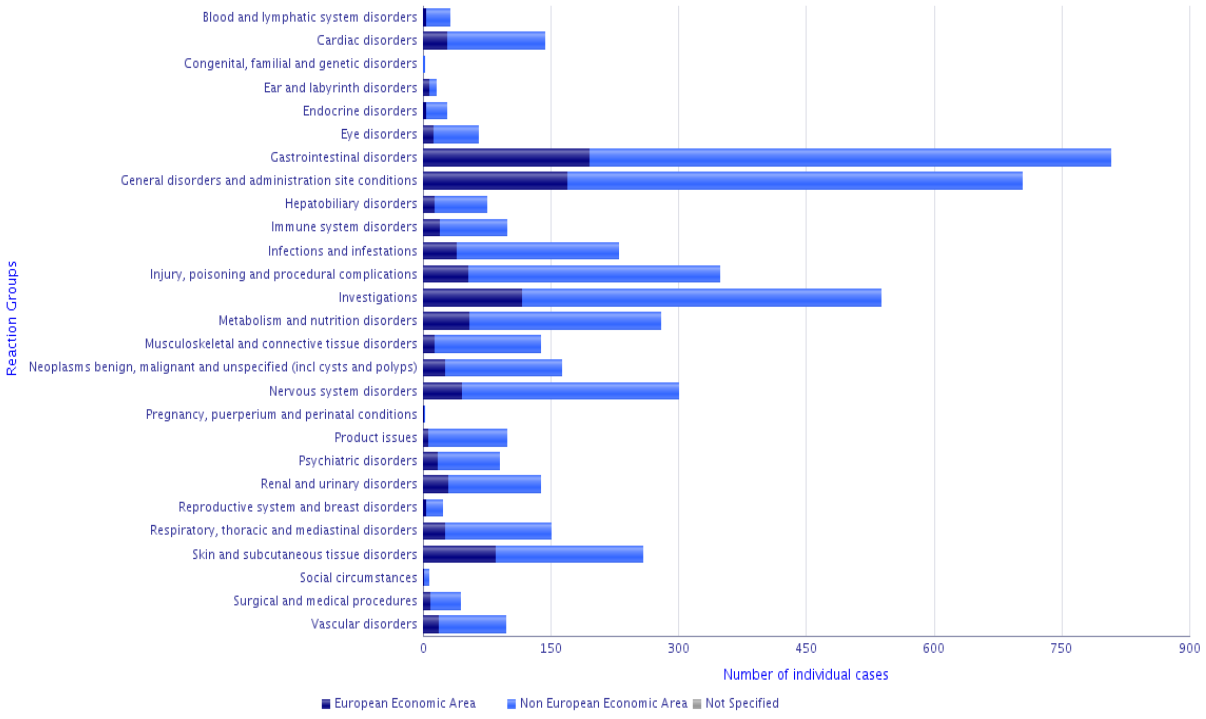

Chart 6 - Number of Individual Cases by Reaction Groups sorted by Geographic Origin in the EU for BYDUREON

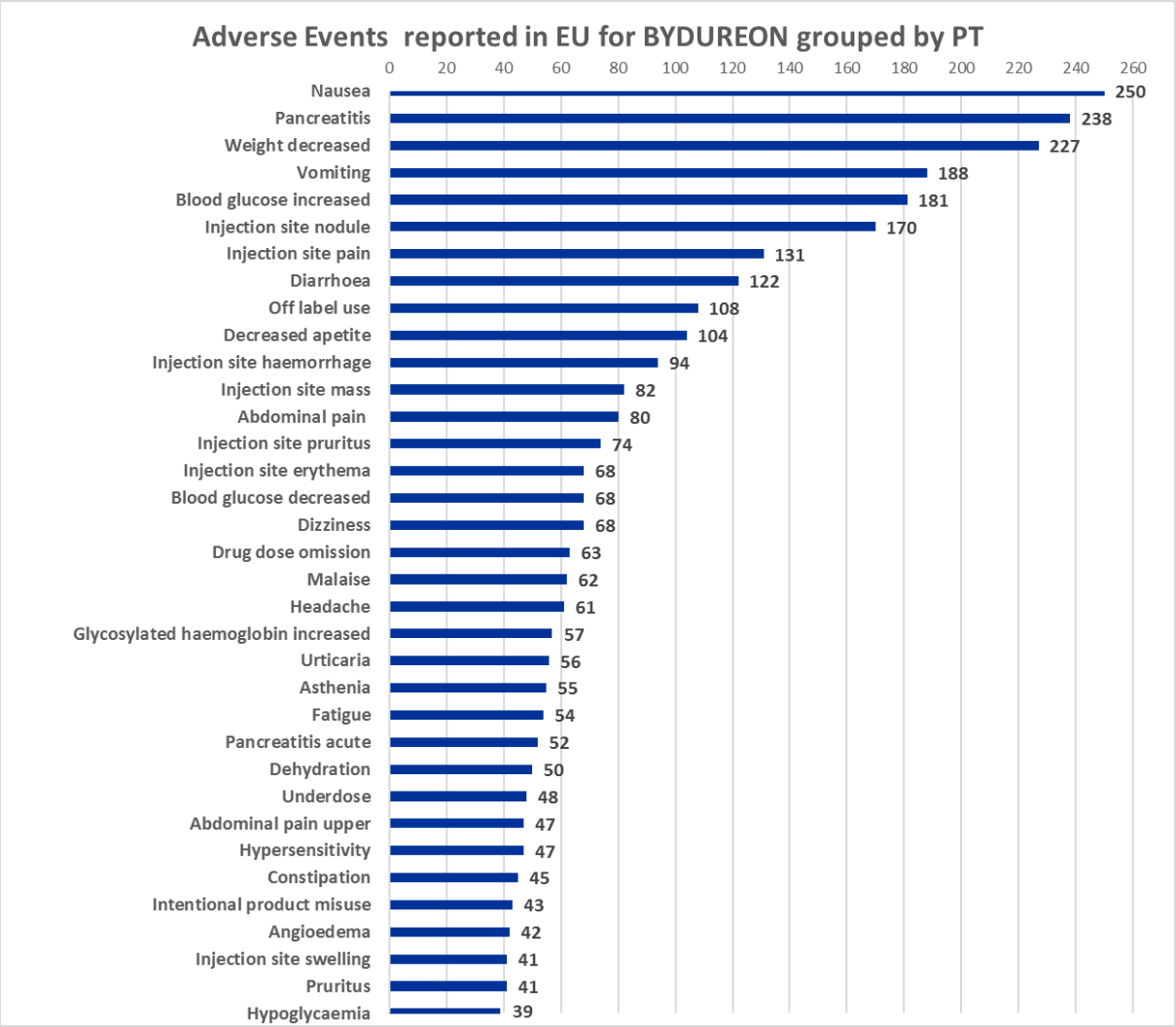

Chart 7 - Adverse Events reported in the EU for BYDUREON grouped by PT

- **FDA Adverse Events Reporting System (FAERS) Data (DrugCite.com)**

The data herein presented was made available by DrugCite database [37]. The results included reports submitted by physicians, healthcare consumers, lawyers amongst others, previously assessed by FDA scientific staff.

The following charts (Chart 8 and Chart 9) illustrate the number of the ADRs reported up to the Q3 2012 to FDA, grouped by SOC and by PT, respectively.

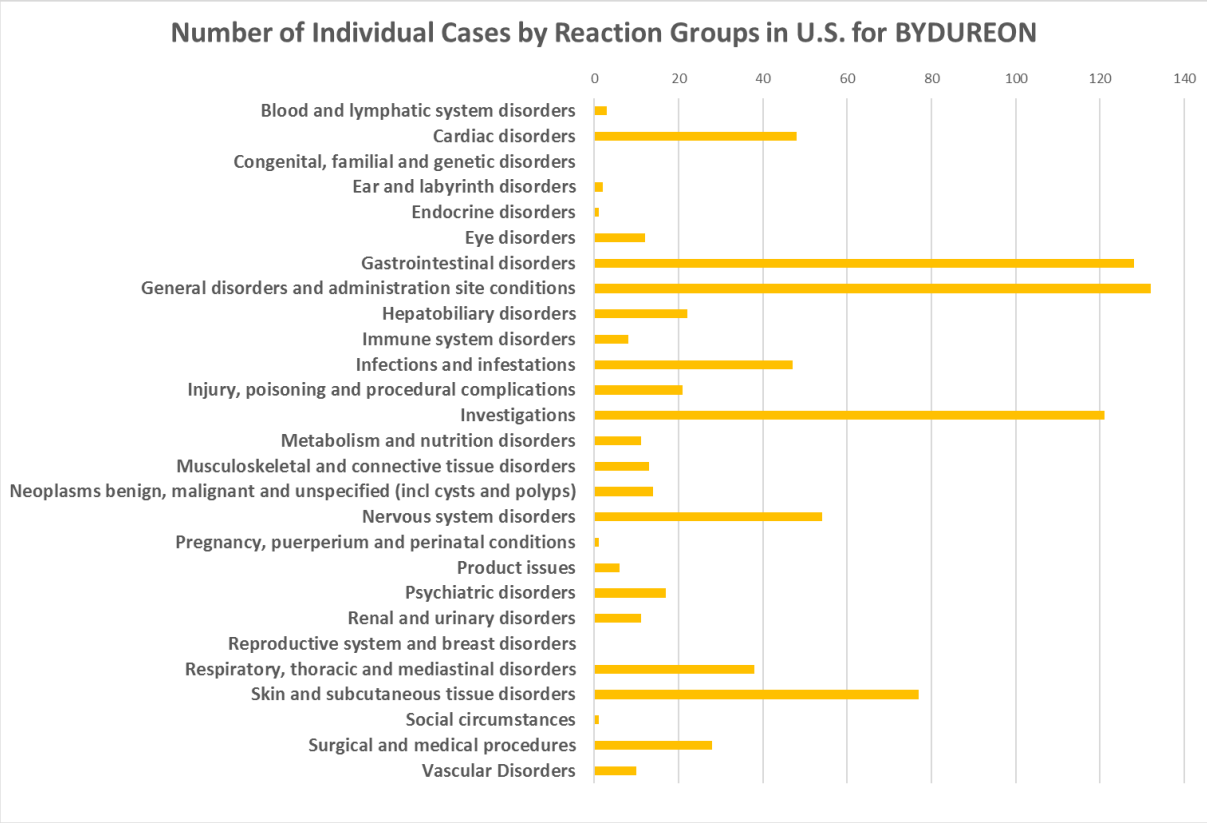

Chart 8 - Number of Individual Cases by Reaction Groups in the U.S. for BYDUREON

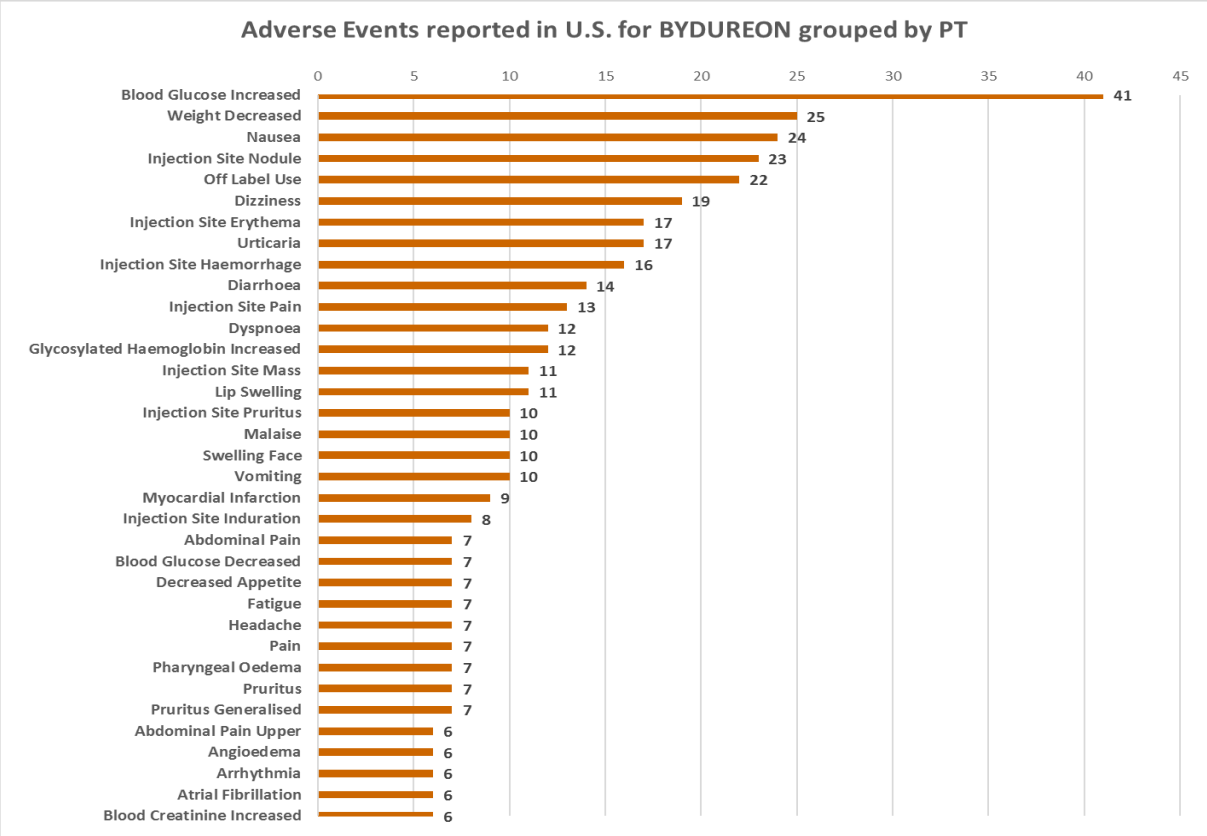

Chart 9 - Adverse Events reported in the U.S. for BYDUREON grouped by PT

- **Comparison of adverse events reported in EU and U.S., grouped by SOC**

Herein it is included a comparison chart regarding the ADRs reported for BYDUREON both in the EU and in the U.S. grouped by SOC.

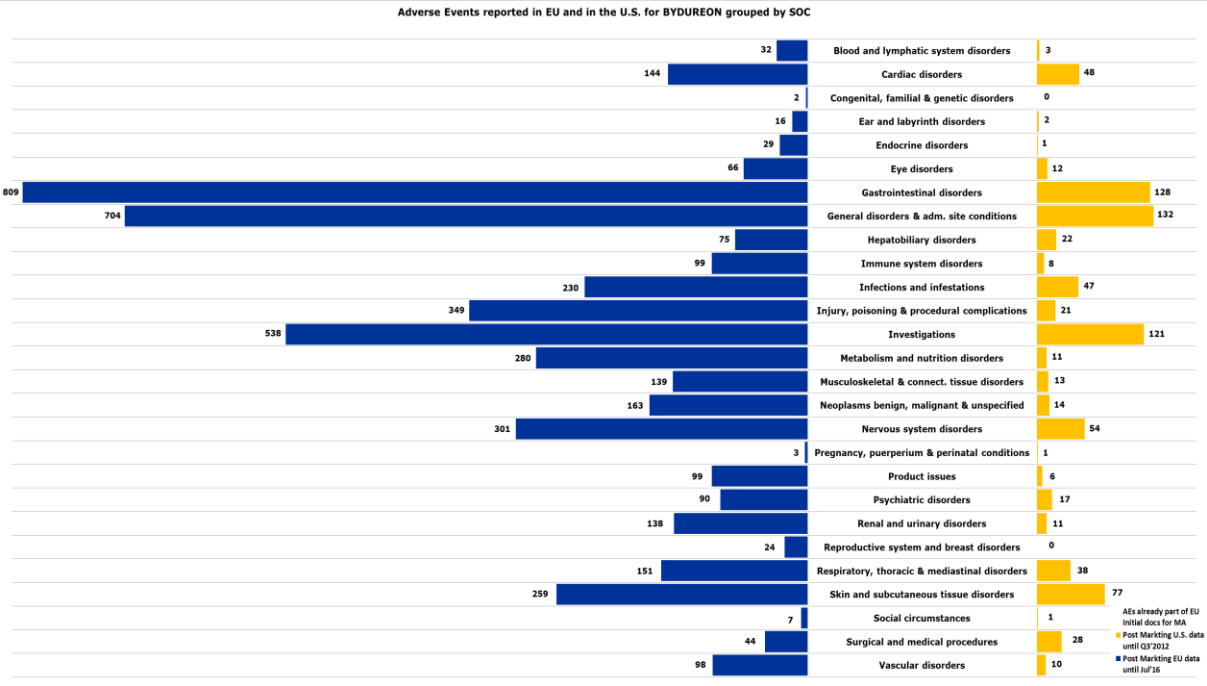

Chart 10 - Adverse Events reported in the EU and in the U.S. for BYDUREON grouped by SOC

Following the analysis of the charts and tables previously presented, it became clear that there were some similarities and some discrepancies between the EU and the U.S. data:

Main similarities:

- Pancreatitis, CV events and renal disorder were identified as risks in both the EU and the U.S..
- GI disorder and *General disorders and administration site conditions SOCs* are the two most prevalent in the EU and in the U.S.. Therefore, GI events, such as nausea, vomiting and diarrhoea, as well as administration site reactions are among the ones most reported in both geographical areas.
- *Nervous system disorders SOC* appears among the most prevalent SOCs, being the 4th most reported in the EU and in the U.S..
- Weight decreased remains in the podium of the most reported events, being the 2nd most reported ADR in the U.S. and the 3rd in the EU.
- Blood glucose increased belongs to the top 5 of the most reported ADRs, having the 1st place in the U.S..

- Regarding anti-exenatide antibodies/immunogenicity, it was identified as a risk in the EU an in the U.S.. Nevertheless, it was not reflected in the post-marketing reports as not being frequently reported.

Main discrepancies:

- Despite the scarcity of data in the U.S., the visual perception allowed by Chart 10 shows that the dispersion of the results trend to be the same, since the most prevalent SOCs are, in a general manner, similar in both sides of the chart.
- GI AEs were identified as risk in the U.S. and severe GI disease was classified as missing information in the EU.
- Hypoglycaemia was identified as a risk in the U.S. but not in the EU. However, in the EU it belongs to the first 35 ADRs reported, not happening the same in the U.S..
- Malignant neoplasms, such as pancreatic cancer and thyroid neoplasms are potential risks in the EU, whereas in the U.S. only the occurrence of an increasing in thyroid tumours are potentially linked with BYDUREON. The prevalence of *Neoplasms benign, malignant and unspecified SOC* is much higher in the EU than in the U.S..
- Pancreatitis belong to the most reported ADRs in the EU not in the U.S..
- In the U.S. *Cardiac disorders* is amongst the most prevalent SOC, being the 6th most reported, whereas in the EU it ranks the 11th place.
- In the U.S. injection site nodules and reactions have been identified as risks associated with the use of BYDUREON, whilst in the EU these were not stated as identified or potential risks for this medicinal product.

BYETTA *VS* BYDUREON

The integrated clinical trial data for exenatide once weekly was carefully examined to identify unique risks associated with the sustained-release formulation. No new risks were identified from the integrated once-weekly clinical trial database, and the identified and potential risks from the existing formulation did not exhibit an unique pattern of occurrence or severity with sustained-release formulation [45].

The short-term safety profile of exenatide QW seem to be largely similar to the BID formulation. However, potential long term effects of the QW dosing are more difficult to evaluate considering the differences in pharmacokinetic profile between the once weekly and the twice daily formulation of exenatide [45].
The marketing authorisation applicant submitted a RMP including both exenatide BID (BYETTA) and exenatide QW (BYDUREON) [45]. Therefore, the table presented below (Table 11) resumes the safety concerns considered for both medicinal products, according to the concerned RMP.

Table 11 - Comparative analysis - BYETTA vs BYDUREON

	BYETTA*[9]	BYDUREON [9]
Safety concerns	**Important Identified risks** - Pancreatitis - Acute Renal failure - Rapid Weight Loss **Important Potential risks** - Risk(s) associated with Anti-Exenatide Antibodies: anaphylactic-type reactions and hypersensitivity - Cardiac events - Malignant Neoplasms: Focus on Pancreatic Cancer and Thyroid Neoplasms. **Missing information** - Adolescents - Pregnant women - Very elderly (≥ 75 years old) - Potential for Concomitant use with TZDs	**Important identified risks** - Pancreatitis - Acute Renal failure - Rapid Weight Loss **Important Potential Risks** - Risk(s) associated with Anti-Exenatide Antibodies: anaphylactic-type reactions and hypersensitivity - Cardiac events - Malignant Neoplasms: Focus on Pancreatic Cancer and Thyroid Neoplasms. **Missing information** - Adolescents - Pregnant women - Very elderly (≥ 75 years old) - Potential for Concomitant use with TZDs - Severe GI disease - Various degrees of impaired renal function - Hepatic impairment.

* In the RMP submitted for BYDUREON, the safety concerns of exenatide BID were updated [9].

It seems important to assess BYETTA and BYDUREON in a stricter manner in order to understand if the extended-release formulation has a relevant role in the expression of any adverse reaction. Therefore, the ADRs reported in the EU are presented in three comparative charts, Chart 11, Chart 12 and Chart 13. The EU data were chosen as in the U.S. the data presented reported only up to the Q3 2012.

- Comparison regarding SOC

Below is presented a single chart comparing the total number of ADRs reported within each SOC for BYETTA and for BYDUREON, up to July 2016.

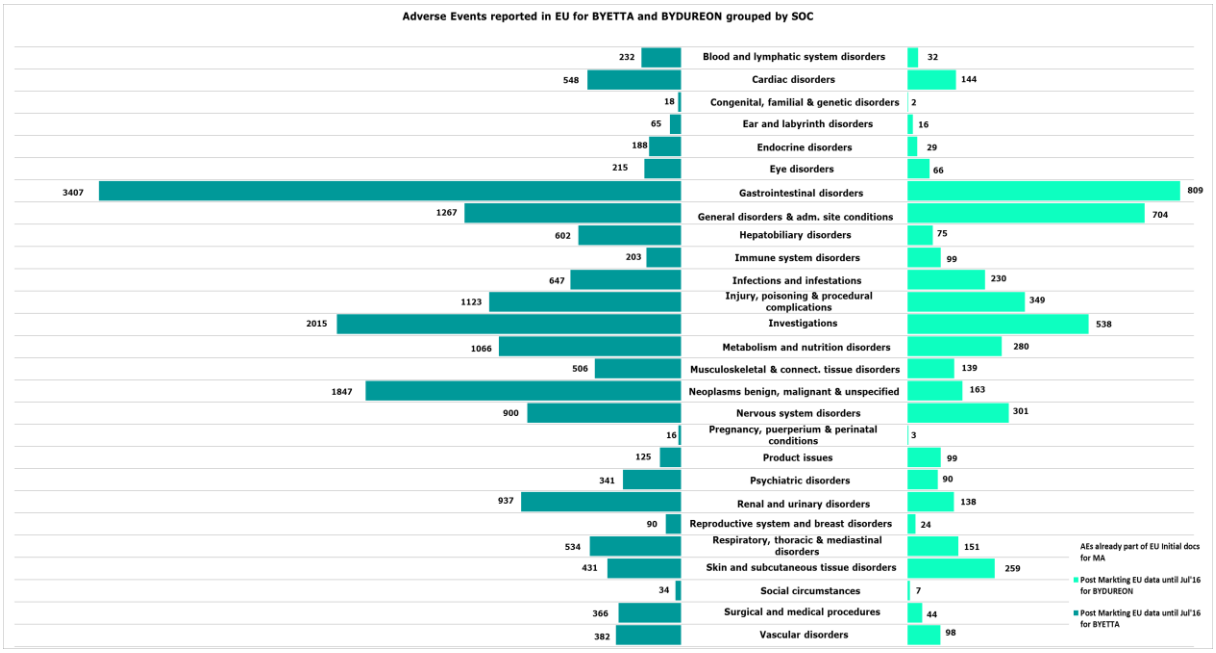

Chart 11 - Adverse Events reported in the EU for BYETTA and BYDUREON grouped by SOC

- ## Comparison regarding PT terms

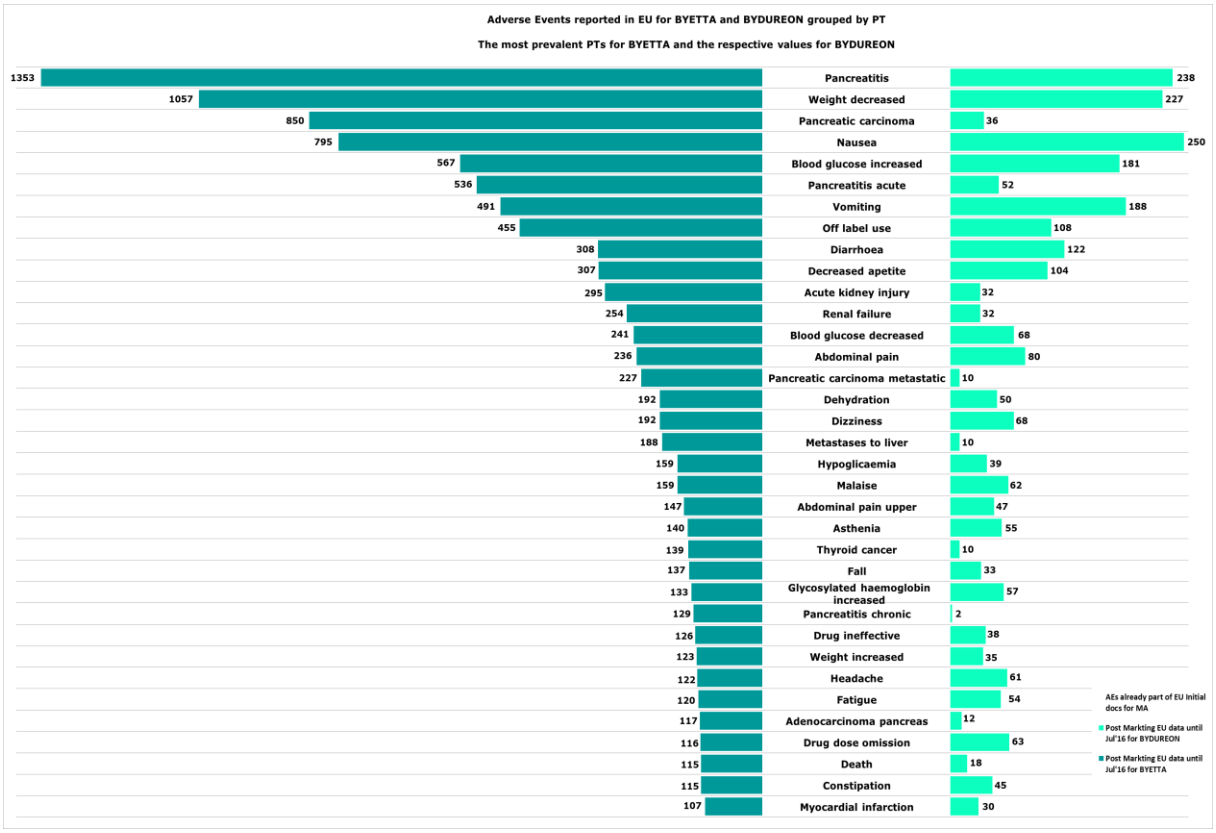

Chart 12 - Adverse Events reported in the EU for BYETTA and BYDUREON grouped by PT. The most prevalent PTs for BYETTA and the respective values for BYDUREON

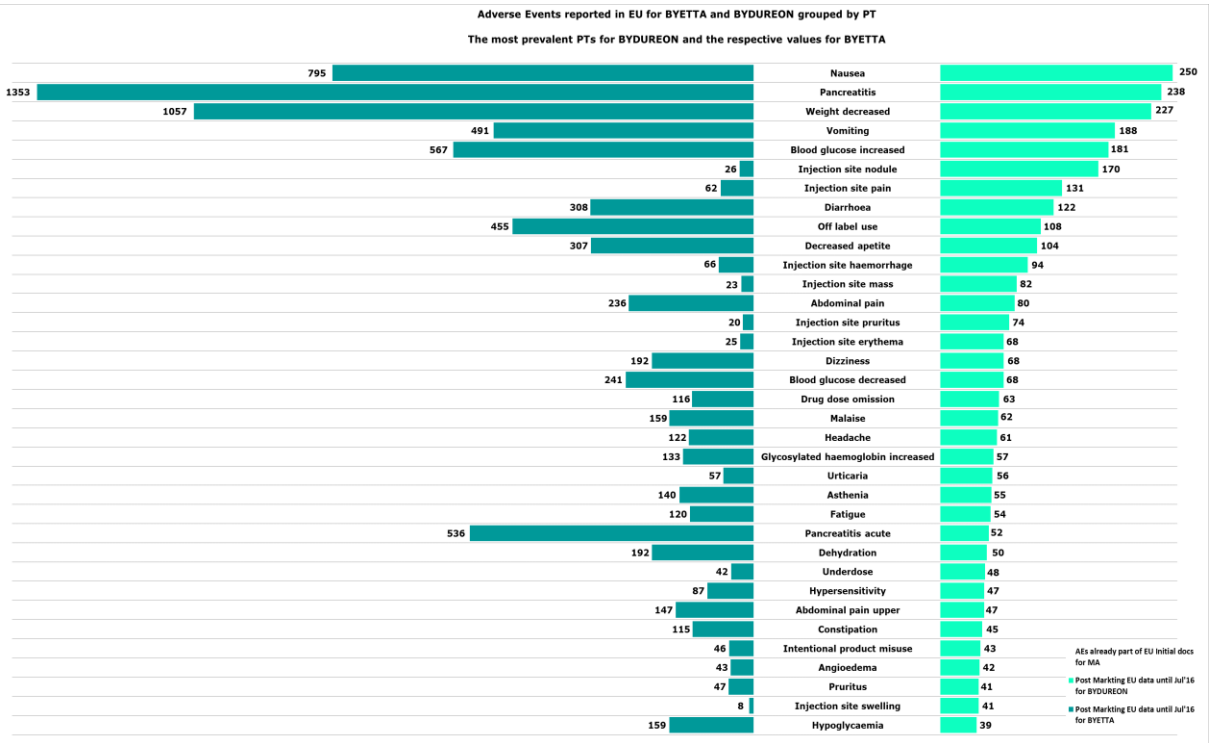

Chart 13 - Adverse Events reported in the EU for BYETTA and BYDUREON grouped by PT. The most prevalent PTs for BYDUREON and the respective values for BYETTA

Following the analysis of the charts and tables previously presented, it became clear that there were some similarities and some discrepancies between BYETTA and BYDUREON safety profile:

Main similarities:

- As previously stated, the BYETTA' safety concerns were updated in the BYDUREON's RMP, since the new data acquired for BYDUREON indicated similarities in the safety concerns to both pharmaceutical formulations. The important and potential risks are the same for both medicinal products.
- *GI disorder SOC* is the most prevalent SOC for both medicinal products. The GI events, such as nausea, vomiting and diarrhoea are among the mostly reported.
- Pancreatitis is an important identified risk. In spite of having much more reports in BYETTA than in BYDUREON, pancreatitis is the most reported ADR with BYETTA and the 2nd most reported with BYDUREON.
- Cardiac events are considered potential risks. *Cardiac disorders SOC* have the same prominence with both medicines, being in the 11th place for BYETTA and BYDUREON.
- Weight decreased remains in the podium of the most reported events, being the 2nd mostly reported ADR with BYETTA and the 3rd with BYDUREON.
- Blood glucose increased occupies the 5th position of the most reported ADRs for both medicinal products.
- Anti-exenatide antibodies/immunogenicity was identified as a potential risk with both medicines. Nevertheless, it was not reflected in the post-marketing reports, as not being frequently reported.

Main discrepancies:

- As previously stated, the BYETTA' safety concerns were updated in the BYDUREON's RMP. The differences remain at the missing information level, as severe GI disease, various degrees of renal function impairment and hepatic impairment were considered for BYDUREON. Regarding the *Hepatobiliary disorders SOC*, its prominence is much higher with BYETTA (10th position) than with BYDUREON (17th position).
- *General disorders and administration site conditions* SOC is the 2nd most prevalent with BYDUREON but not with BYETTA. In accordance with this, administration site reactions are the mostly reported with BYDUREON and they are among the less reported with BYETTA.
- Acute renal failure is an important identified risk for both medicines. Nevertheless, it is possible to see that the SOC *Renal and urinary disorders* has more prevalence with BYETTA than with BYDUREON, having the 7th and the 11th places respectively.
- Malignant neoplasms, with focus on pancreatic cancer and thyroid neoplasms, are important identified risks for both medicinal product. However, and in line with what is seen for renal disorders, the prevalence of the *Neoplasms benign, malignant and unspecified SOC* is much higher with BYETTA (3rd place in prevalence) than with BYDUREON (9th place). Accordingly, pancreatic carcinoma is the 3rd ADR with more reports in BYETTA, and if pancreatic carcinoma metastatic is added it moves to the 2nd position. Additionally, thyroid cancer belongs to the top 35 of the most reported ADRs for BYETTA. For BYDUREON these reactions are not among the mostly reported as occurs to BYETTA.
- BYETTA had a marketing authorisation granted in 2006 in the EU while BYDUREON only had marketing authorisation granted five years later, in 2011. Thus, BYETTA has much more post-marketing data than BYDUREON, which may bias the analysis. Nonetheless, the visual perception enabled by Chart 11 lead to hypothesised that if a dispersion curve is imagined the trend could be similar if the same number of BYETTA reports would be achieved by BYDUREON, with the exception of *General disorders and administration site conditions* and *Renal and urinary disorders SOC.*

VICTOZA

VICTOZA is a 6 mg/ml solution for injection in a pre-filled pen once a day. Its active substance is liraglutide. Liraglutide is a long-acting analogue of the naturally occurring human GLP-1 with 97% homology and a lipophilic substituent for prolongation of half-life. This analogue is produced using the recombinant DNA technology in Yeast (*Saccharomyces cerevisiae*). Unlike GLP-1, liraglutide has a pharmacokinetic and pharmacodynamics profile in human suitable for once daily administration. Thus, liraglutide is administered once daily subcutaneously for the convenience of the patient and to improve compliance. Following SC administration, the protracted action profile is based on three mechanisms: self-association, which results in slow absorption, and binding to albumin and enzymatic stability towards the DPP-4 enzyme both resulting in a prolonged plasma half-life [47].

These medicinal product is approved in monotherapy and in several therapeutic combinations, as identified in Table 4 - Approved therapeutic indications.

Regarding the VICTOZA' safety profile, comparative analyses are presented. A comparison between safety information included in EPAR (nonclinical and clinical data) and in RMP is presented in Table 12. Table 13 resumes the safety concerns considered by EMA and those ones accepted by FDA.

Table 12 - Comparative analysis on VICTOZA' safety profile

	Nonclinical data [47]	Clinical data [47]	RMP data [39]
Safety concerns	**Mice/ Rat/ Monkey:** - Decreased body weight gain and food consumption **Cardiotoxicity:** Rat: - Increases in blood pressures and heart rate (dose-related) **Carcinogenicity:** Mice - C-cell tumours - Uterus leioma and leiosarcoma - Skin sarcomas increased (high dose) Rat: - C-cell tumours (longer studies) Monkey: - Increased pancreatic weight (increased duct cell mass and exocrine cells) - No C-cell hyperplasia and changes in C-cell mass **Antigenicity/ Immunogenicity:** Monkey: - Antibodies found (immunological reaction possible) **Reproduction Toxicity** Rat: - Decreased weight gain - crosses the placental barrier Rabbit: - Large decrease in food consumption (embryofoetal toxicity studies) - crosses the placental barrier Dog: - Secreted into dog breast milk - amount that a pup would receive per day via breast milk is low (at most 3% of the maternal dose) **Local tolerance** Pig: - Subacute inflammation in the injection site tissue Rat/ Monkey - Effects at the injection site (repeat dose toxicity studies) **Immunotoxicity** - No studies performed→ no relevant findings on the immune system organs observed in repeat dose studies.	**Identified safety issues** - Hypoglycaemia - GI AEs including nausea, diarrhoea, vomiting, constipation, dyspepsia **Potential Safety Issues** - Medullary Thyroid cancer - Neoplasm - Cardiac co-morbidity - Late stage microvascular complication of the eye - Immunogenicity (antibody formation, allergic reactions and injection site disorders) - Pancreatitis **Missing information** - Abuse due to weight lowering potential - Children and adolescents - Overdose - Pregnant and lactating women - Potential interaction with warfarin - Cardiac co-morbidity - Renal and hepatic impairment/endstage renal failure - Off-label use	**Important Identified risks** - Hypoglycaemia - GI AEs: nausea, diarrhoea, vomiting, constipation and dyspepsia **Important Potential risks** - Medullary thyroid cancer (c-cell carcinogenicity) - Neoplasms - Pancreatitis - Immunogenicity – antibody development and allergic reactions - Injection site disorders - Cardiac co-morbidity - Late stage microvascular eye complication **Missing information** - Pregnant and lactating women - Children and adolescents <18 years - Overdose - Abuse due to weight lowering potential - Congestive heart failure NYHA I-IV - Drug-drug interaction with warfarin - Benefit-risk in patients with hepatic or renal impairment/end stage renal disease - Off-label use

Table 13 - Summary of safety concerns considered by EMA and FDA for VICTOZA

	EMA	FDA [46] [48]
Safety concerns	**Important Identified risks** - Hypoglycaemia - GI AEs: nausea, diarrhoea, vomiting, constipation and dyspepsia **Important Potential risks** - Medullary thyroid cancer (c-cell carcinogenicity) - Neoplasms - Pancreatitis - Immunogenicity – antibody development and allergic reactions - Injection site disorders - Cardiac co-morbidity - Late stage microvascular eye complication **Missing information** - Pregnant and lactating women - Children and adolescents <18 years - Overdose - Abuse due to weight lowering potential - Congestive heart failure NYHA I-IV - Drug-drug interaction with warfarin - Benefit-risk in patients with hepatic or renal impairment/end stage renal disease - Off-label use	- GI AEs, e.g. nausea, vomiting and diarrhoea. - Anti-drug antibody formation – Hypersensitivity reactions - Injection site reactions - Hypoglycaemia - Medullary thyroid cancer - Pregnancy and lactation - Major adverse CV events - QT prolongation - Pancreatic issues: pancreatitis or pancreatic cancer - Dose-related carcinogenic potential

- European database of suspected adverse drug reaction reports

The data herein presented was retrieved from European database adrreports.eu [36]. This website gives access to web reports on suspected ADRs by medicine or by active substance name. All the data displayed in the web reports is taken from EudraVigilance, a system designed for collecting reports of ADRs occurred within and outside the EEA [36]. This includes reports received from healthcare professionals and patients, reported by national competent authorities and MAHs.

The following charts (Chart 14 and Chart 15) illustrate the number of the ADRs reported up to July 2016 to EudraVigilance, grouped by SOC and by PT, respectively.

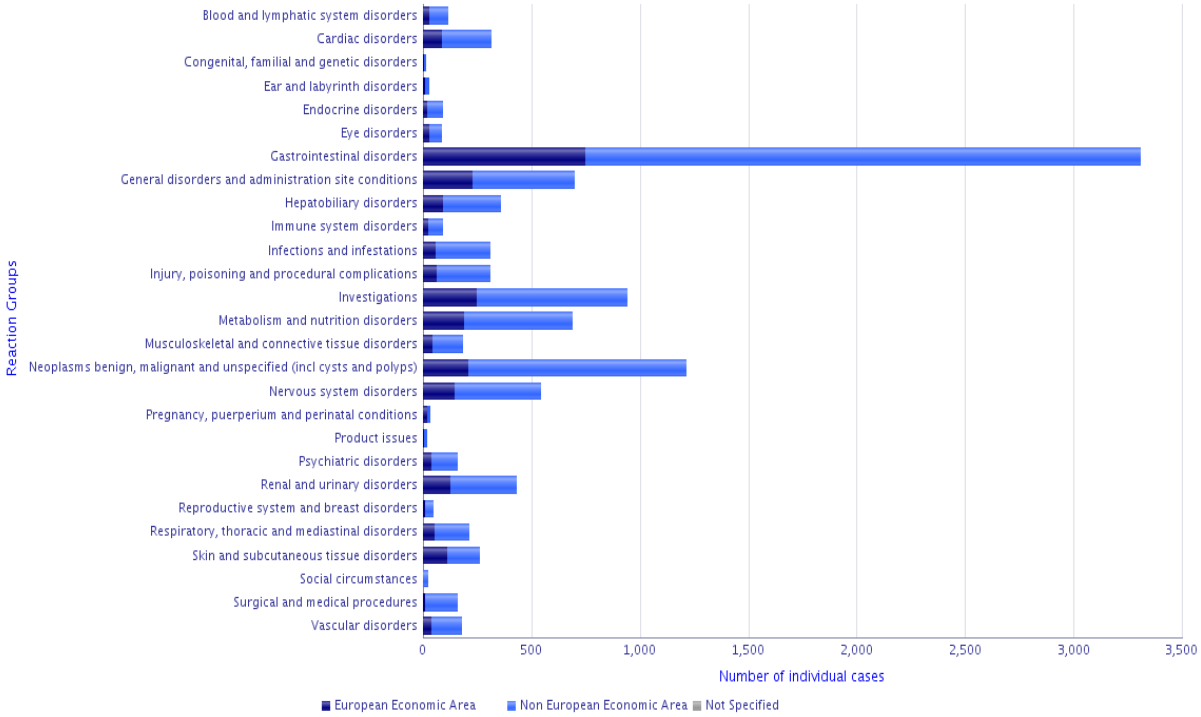

Chart 14 - Number of Individual Cases by Reaction Groups sorted by Geographic Origin in the EU for VICTOZA

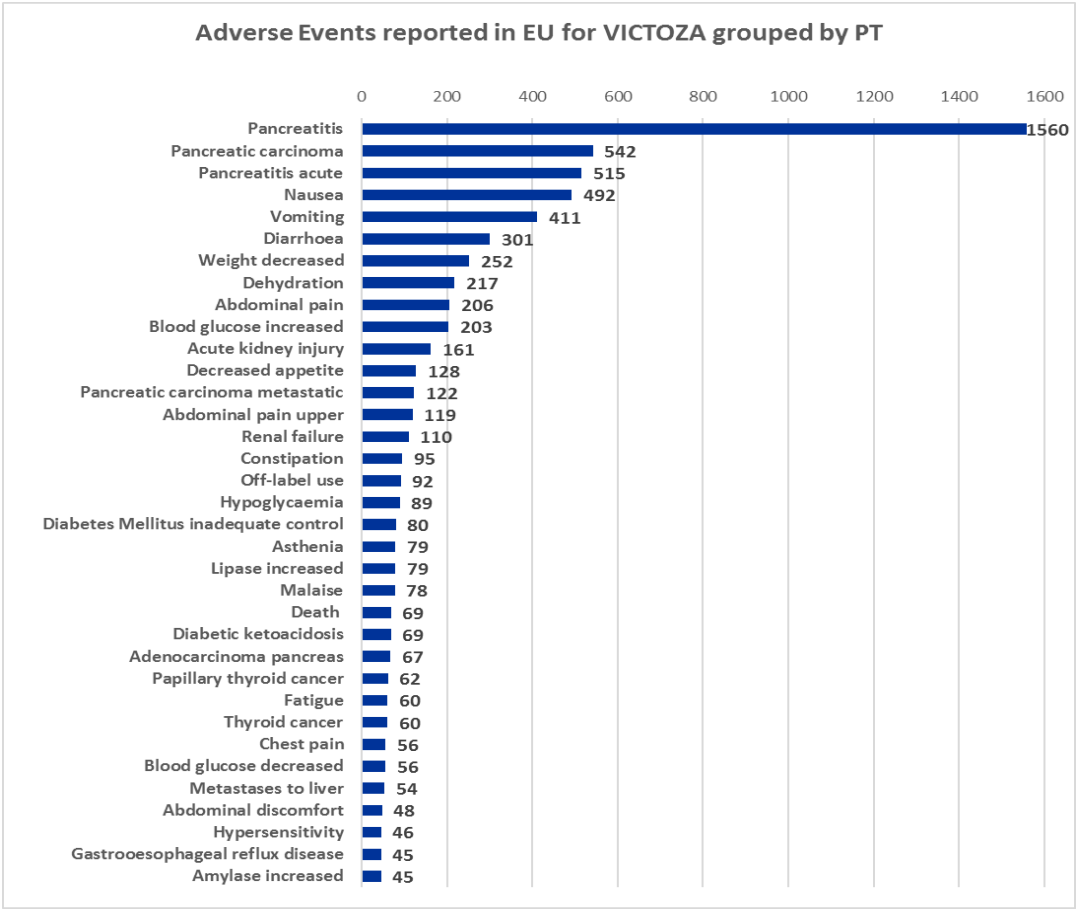

Chart 15 - Adverse Events reported in the EU for VICTOZA grouped by PT

- **FDA Adverse Events Reporting System (FAERS) Data (DrugCite.com)**

The data herein presented was made available by DrugCite database [37]. The results included reports submitted by physicians, healthcare consumers, lawyers amongst others, previously assessed by FDA scientific staff.

The following charts (Chart 16 and Chart 17) illustrate the number of the ADRs reported up to the Q3 2012 to FDA, grouped by SOC and by PT, respectively.

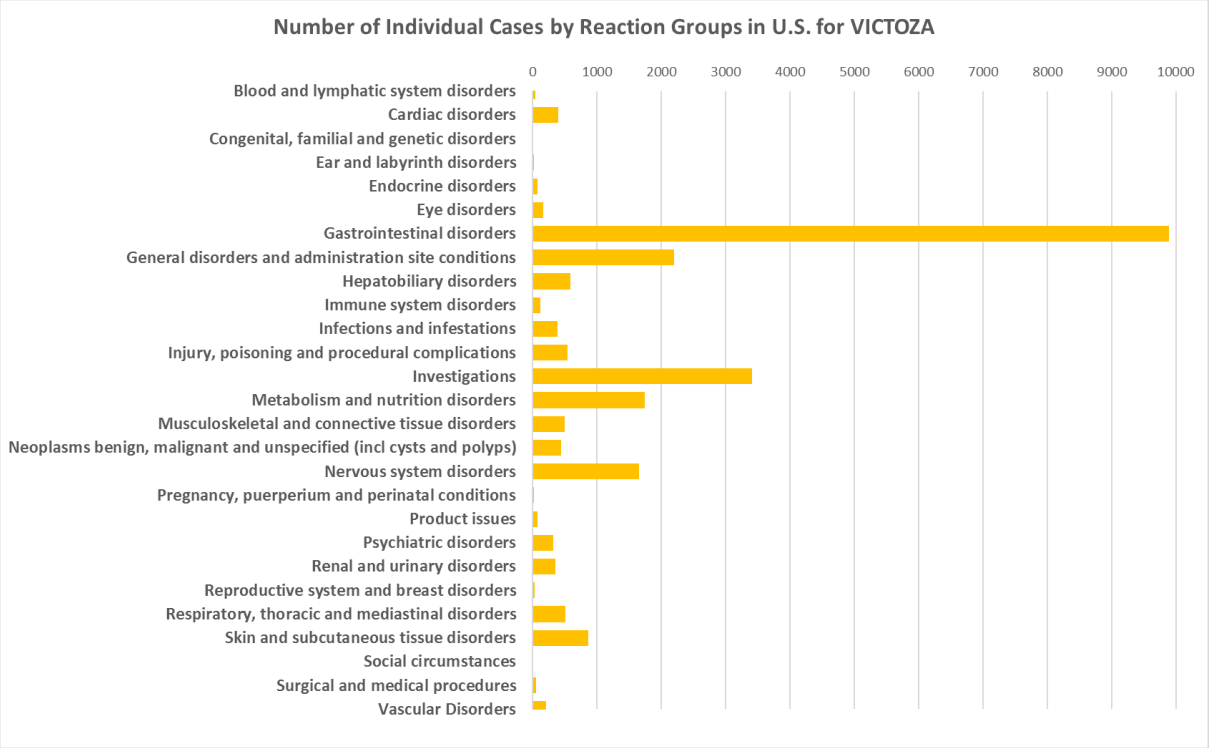

Chart 16 - Number of Individual Cases by Reaction Groups in the U.S. for VICTOZA

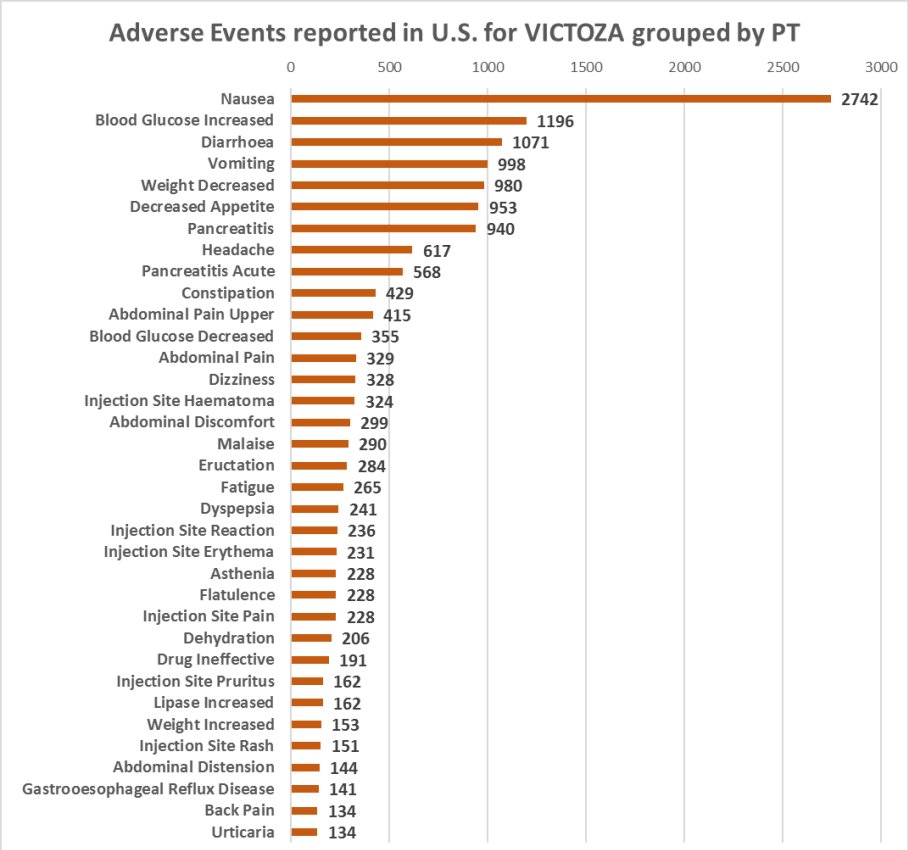

Chart 17 - Adverse Events reported in the U.S. for VICTOZA grouped by PT

- **Comparison of adverse events reported in the EU and in the U.S., grouped by SOC**

Herein it is included a comparison chart regarding the ADRs reported for VICTOZA both in the EU and in the U.S. grouped by SOC.

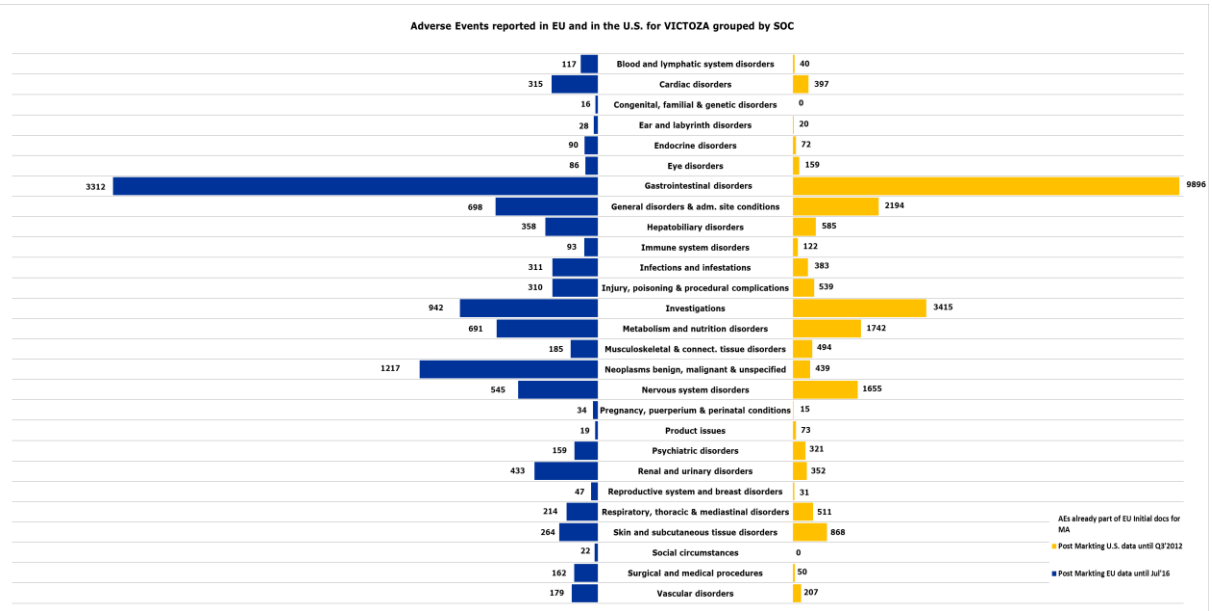

Chart 18 - Adverse Events reported in the EU and in the U.S. for VICTOZA grouped by SOC

Following the analysis of the charts and tables previously presented, it became clear that there were some similarities and some discrepancies between the EU and the U.S. data:

Main similarities:

- Hypoglycaemia is considered a risk both in the EU and in the U.S.. Hypoglycaemia and blood glucose decreased have been reported across the EU and in the U.S..
- GI AEs, such as nausea, diarrhoea, vomiting, constipation and dyspepsia are important identified risks associated with VICTOZA. Accordingly, *GI disorder SOC* is the SOC with the major number of cases reported in the EU and in the U.S., and so these reactions are among the ones most reported.
- Pancreatitis belong to the list of potential risks associated with the use of VICTOZA, both in the EU not in the U.S. This risk is corroborated by the real-world data, since represents the 1st ADR mostly reported in the EU and is also among the ADRs mostly reported in the U.S.
- Weight decreased are not identified as risk to VICTOZA but it remains one of the most reported reactions, being the 5th mostly reported ADR in the U.S. and the 7th in the EU.
- Blood glucose increased not considered as a risk, is the 2nd reaction mostly reported in the U.S. and the 10th in the EU.
- *Nervous system disorders SOC* appears among the most prevalent SOCs both in the U.S. and in the EU.
- Regarding immunogenicity and hypersensitivity reactions, they were identified as risks in the EU an in the U.S.. Nevertheless, they were not reflected in the post-marketing reports as not being frequently reported.
- Injection site reactions were identified in the pre-marketing phase as being risks for this medicinal product in the EU and in the U.S..
- By the visual perception allowed by Chart 18 it is possible to conclude that the data dispersion trend to be similar in the EU and in the U.S.. In general, the SOC mostly

prevalent in the EU trend to be the same in the U.S., except for the SOC *Neoplasms benign, malignant and unspecified* which is the major discrepancy.

Main discrepancies:

- Malignant neoplasms, such as pancreatic cancer and thyroid neoplasms are potential risks in the EU and in the U.S., but the post-marketing prevalence is higher in the EU and not in the U.S.. The SOC *Neoplasms benign, malignant and unspecified* is the 2nd most prominent in the EU and belongs to the less reported in the U.S.. Moreover, concerning the PTs charts, pancreatic carcinoma is the 2nd most reported and thyroid carcinomas are also presented in the top 35 ADRs in the EU, while in the U.S. no carcinomas are presented in the top 35.
- CV events were considered risks for this medicinal product in the both geographical areas. However, the prevalence in the EU is superior than the prevalence in the U.S., as the SOC *Cardiac disorders* is on the 9th position of prevalence whereas in the U.S. it is on the 12th position.
- On the basis of the charts results, *General disorders and administration site conditions SOC* is the 3rd most reported in the U.S. and the 4th in the EU. Regarding the PTs, injection site reactions are often reported in the U.S. but they are not in the EU.

LYXUMIA / ADLYXIN

LYXUMIA is an antidiabetic medicine that contains the active substance lixisenatide. It is available as a solution for injection in a pre-filled pen that provides either 10 mcg or 20 mcg of lixisenatide in each dose. It is subcutaneously administered once a day, within the hour prior to the first meal of the day or the evening meal. [27, 41]

Lixisenatide is a GLP-1R agonist resistant to enzymatic cleavage by DPP-4. This results in a longer duration of action enabling the use lixisenatide for therapeutic purposes. The recommended maintenance dose is 20 mcg once daily; which is achieved after a 2-week starting regimen of lixisenatide 10 mcg once daily [25].

Lixisenatide is a synthetic peptide containing 44 amino acids, which is amidated at the C-terminal amino acids. This active substance had a binding affinity approximately 4 times greater than native human GLP-1 to GLP-1R [25].

These medicinal product is approved in several therapeutic combinations, as identified in Table 4 - Approved therapeutic indications.

Specific safety issues related to potential risks of medullary thyroid cancer, pancreatitis, malignant neoplasms, propensity to induce a transient increased heart rate, and malformations observed in animal development studies have been evaluated and are addressed in SmPC and /or RMP [49]. The following table (Table 14) encompasses the comparative analyses regarding the safety profile of LYXUMIA between information included in EPAR and in RMP.

Table 14 - Comparative analysis on LYXUMIA' safety profile

	Nonclinical data [25]	Clinical data [25]	RMP data [39]
Safety concerns	Rat: - Testicular and epididymal effects (high dose): atrophy, spermatid stasis and mineralisation in the testis and oligospermia and aspermia in the epididymis - Limited increase in mean arterial blood pressure. Dog: - Reversible testicular and epidydimal toxicities. **Carcinogenicity:** Rat: - Proliferative effects on thyroid C-cells Mice: - Proliferative effects on thyroid C-cells **Reproduction Toxicity** Rat: - Microphthalmia, anophthalmia, diaphragm hernia and multiple skeletal malformations - Retardation of foetal growth and ossification (dose-dependent) - Maternal toxicity: decreased motor activity, piloerection, decreased body weight and food consumption Rabbits: - Multiple malformations - Skeletal and visceral anomalies and retarded ossification **Antigenicity/ Immunogenicity** Mice/ rat/ dog: - Antidrug antibodies → pharmacokinetics with higher exposures	**Important identified risks** - GI events i.e. nausea, vomiting - Systemic hypersensitivity reactions - Hypoglycaemia, when used with a SU or basal insulin **Important potential risks** - CV events - Acute pancreatitis - Medullary thyroid cancer - Malignant neoplasm - Immunogenicity / Neutralization - Dehydration / Acute renal impairment - - Off-label use in non-T2DM for weight loss - Teratogenicity **Missing information** - Use in pregnant women - Use in lactating women - Use in children and adolescents <18 years - Use in very elderly (≥75 years) - Use in patients with moderate and severe renal impairment (with and without low body weight)	**Important identified risks** - GI events i.e. nausea, vomiting - Systemic hypersensitivity reactions - Hypoglycaemia, when used with a SU or basal insulin **Important potential risks** - CV events - Acute pancreatitis - Medullary thyroid cancer - Malignant neoplasm - Immunogenicity / Neutralization - Dehydration - Acute renal impairment - Off-label use in non-T2DM for weight loss - Teratogenicity **Missing information** - Use in pregnant women - Use in lactating women - Use in children and adolescents <18 years - Use in very elderly (≥75 years) - Use in patients with moderate and severe renal impairment (with and without low body weight)

Table 15 - Summary of safety concerns considered by EMA and FDA for LYXUMIA / ADLYXIN

	EMA	FDA [50]
Safety concerns	**Important identified risks** - GI events i.e. nausea, vomiting - Systemic hypersensitivity reactions - Hypoglycaemia, when used with a SU or basal insulin **Important potential risks** - CV events - Acute pancreatitis - Medullary thyroid cancer - Malignant neoplasm - Immunogenicity / Neutralization - Dehydration / Acute renal impairment - Off-label use in non-T2DM for weight loss - Teratogenicity **Missing information** - Use in pregnant women - Use in lactating women - Use in children and adolescents <18 years - Use in very elderly (≥75 years) - Use in patients with moderate and severe renal impairment (with and without low body weight)	- GI events (i.e. mainly nausea and vomiting) - Hypoglycaemia increased when used with SU or insulin - Immunogenicity - Hypersensitivity - Pancreatitis - Renal impairment in patients with severe GI reactions - Medullary thyroid cancer - Other malignancies

- European database of suspected adverse drug reaction reports

The data herein presented was retrieved from European database adrreports.eu [36]. This website gives access to web reports on suspected ADRs by medicine or by active substance name. All the data displayed in the web reports is taken from EudraVigilance, a system designed for collecting reports of ADRs occurred within and outside the EEA [36]. This includes reports received from healthcare professionals and patients, reported by national competent authorities and MAHs.

The following charts (Chart 19 and Chart 20) illustrate the number of the ADRs reported up to July 2016 to EudraVigilance, grouped by SOC and by PT, respectively.

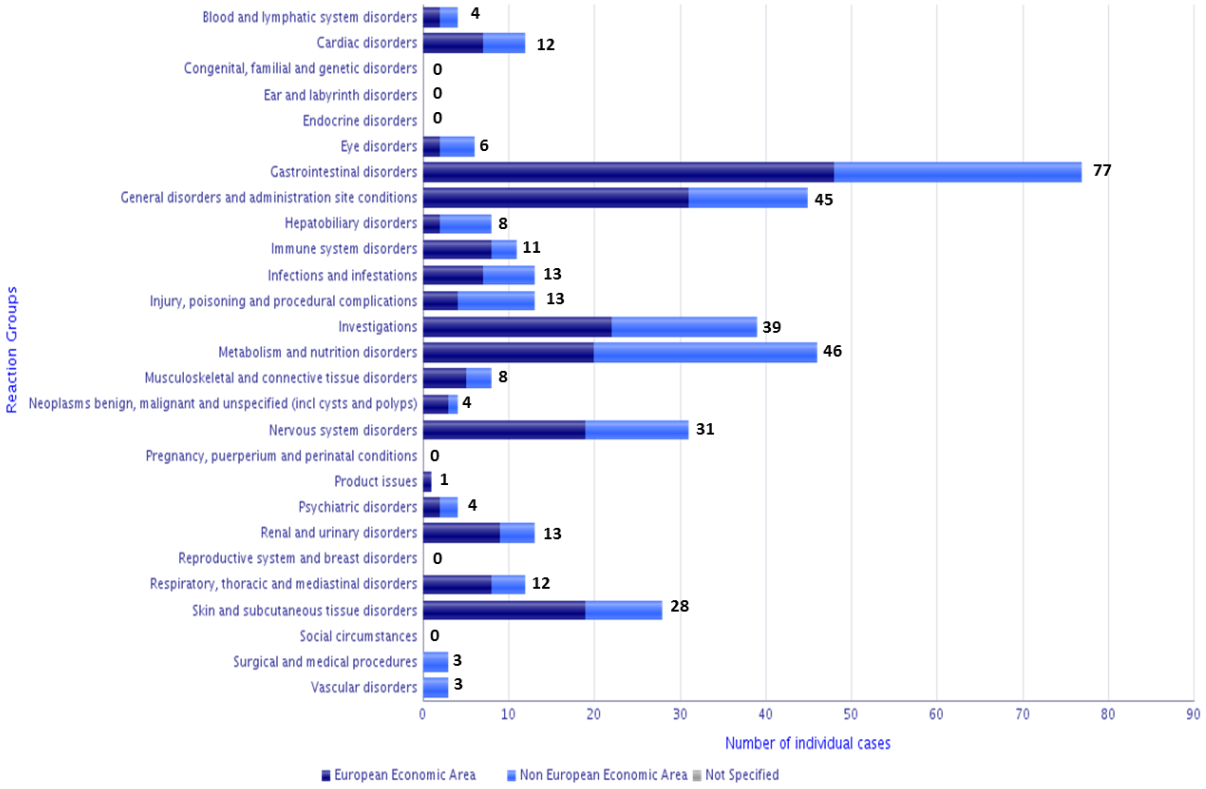

Chart 19 - Number of Individual Cases by Reaction Groups sorted by Geographic Origin in EU for LYXUMIA

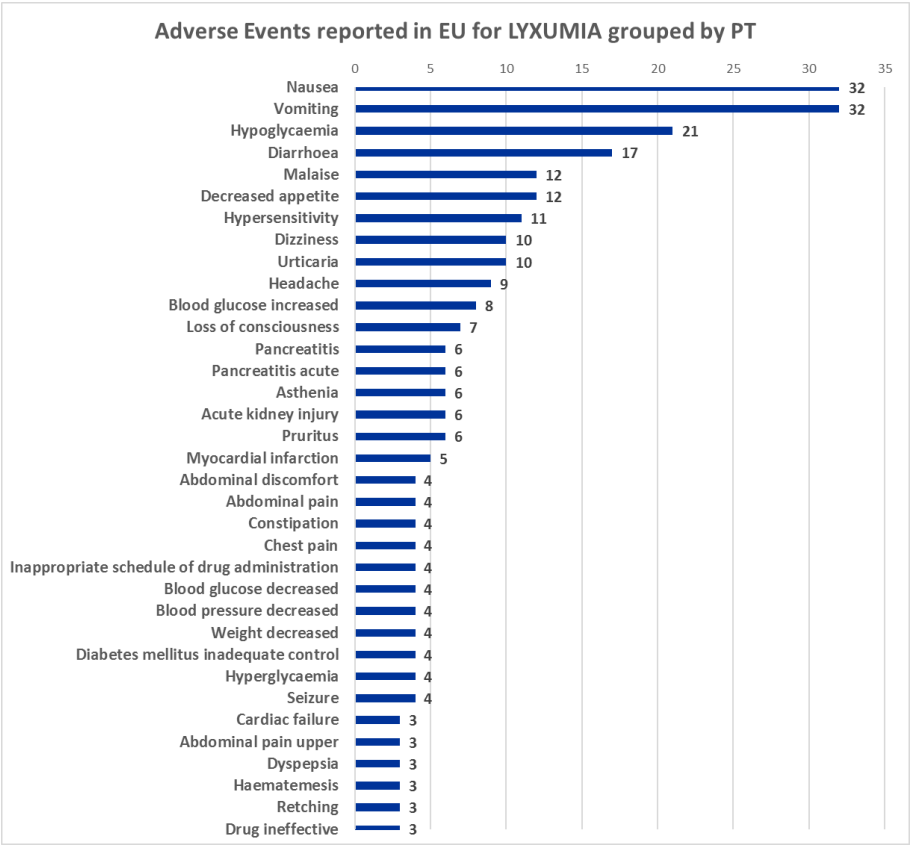

Chart 20 - Adverse Events reported in EU for LYXUMIA grouped by PT

- **FDA Adverse Events Reporting System (FAERS) Data (DrugCite.com)**

This database includes information regarding the number of the ADRs reported since the authorisation date up to the Q3 2012 to FDA. As ADLYXIN was only approved in 2016 in U.S., there is no data available.

- **Comparison of adverse events reported in EU and U.S., grouped by SOC**

As no data is available from FDA, it was not possible to perform this comparison.

As aforementioned, it is no possible to perform a comparison between the post-marketing data in the EU and in the U.S., as no U.S. data are available. However, on the basis of the charts and tables previously presented, it is possible to perform the following analysis:

- GI AEs, such as nausea and vomiting are important identified risks both in the EU and in the U.S.. Accordingly, in the EU, *GI disorder SOC* is the SOC with the major number of cases reported, and nausea and vomiting are the 1st and 2nd most reported ADRs, respectively.
- Hypoglycaemia is considered a risk, in the EU and in the U.S., when used with a SU or basal insulin. Regarding the PT chart, it is possible to see that hypoglycaemia is the 3rd ADR most frequently reported with LYXUMIA.
- In the EU, systemic hypersensitivity reactions were identified as important identified risks. For ADLYXIN, in the U.S., hypersensitivity was also considered a risk. According to the post-marketing available data, hypersensitivity remains in the top 10 of the most reported ADRs.
- CV events were considered potential risks for this medicinal product just in the EU. When analysing the post-marketing data, it is possible to realize that, up to the moment, the occurrence of such events is not higher, as the *Cardiac disorder SOC* has only 12 cases reported.
- Acute pancreatitis belongs to the list of potential risks associated with the use of LYXUMIA, in the EU. Similarly, in the U.S. pancreatitis is also considered a risk. According to the PT chart, up to July 2016 there were 6 cases of pancreatitis and 6 of pancreatitis acute associated with the use of LYXUMIA.
- Malignant neoplasms is a potential risks for this medicinal product. Per the SOC chart, the SOC *Neoplasms benign, malignant and unspecified* has a very low prevalence (4 cases), being among the less reported, and there is no carcinoma PTs among the to 35.
- Immunogenicity/neutralization are considered potential risks for this medicinal product both in the EU and in the U.S.. Moreover, in the U.S. hypersensitivity reactions were also included in the risk list. Based on the charts results, this is not verified.
- Acute renal impairment is an important potential risk in the EU.In the U.S. renal impairment in patients with severe GI reactions was also included as a risk.

Accordingly, to the data presented in the charts, these are verified as *Renal and urinary disorders SOC* have a moderate prevalence, and acute kidney injury presented 6 cases.

- Dehydration is also addressed as a potential risk only in the EU. Nevertheless, this PT is not presented among the 35 mostly reported.
- Weight decreased is not identified as risk to LYXUMIA but it is presented in the top 35 of the most reported PTs. Once this outcome is occurring in patients who use LYXUMIA, there was identified the potential risk off-label use in non-T2DM for weight loss.
- Teratogenicity is also a potential risk in the EU. However, it is not corroborated by the post-marketing data, as no reports were identified in the *SOC Congenital, familial and genetic disorders*.
- Blood glucose increased not considered as a risk, it has the 11th place of the most PTs reported.
- *Nervous system disorders SOC* appears among the most prevalent SOCs.

EPERZAN/ TANZEUM

The active substance of EPERZAN/TANZEUM is albiglutide, available in the pharmaceutical form of powder and solvent for solution for injection, administered subcutaneously once a week.

Albiglutide is a GLP-1R agonist generated by fusion of GLP-1 analogue to albumin [28]. Albiglutide is produced in *Saccaromyces cerevisiae* by recombinant DNA technology. It is a recombinant fusion protein consisting of two copies of a 30-amino acid sequence of modified human GLP-1 genetically fused in series to human albumin (97% amino acid sequence homology to endogenous human GLP-1 fragment 7-36). The GLP-1 sequence has been modified to confer resistance to DPP-4 mediated proteolysis. The human albumin moiety of the recombinant fusion protein, together with the DPP-4 resistance, greatly extends the half-life to 5 day allowing once weekly dosing [51].
These medicinal product is approved in monotherapy and in several therapeutic combinations, as identified in Table 4 - Approved therapeutic indications.

The following tables (Table 16 and Table 17) encompass the comparative analyses regarding the safety profile of EPERZAN, either between information included in EPAR and in RMP as well as between the safety concerns accepted by EMA and by FDA.

Table 16 - Comparative analysis on EPERZAN' safety profile

	Nonclinical data [51]	Clinical data [51]	RMP data [11]
Safety concerns	**Toxicology** Monkey: - No CV effects nor effects in respiratory function. - Increased pancreas weight (more in males than in females) and significant increase in islet cell number. **Carcinogenicity** - No carcinogenicity studies have been conducted due to immunogenicity: emergence of clearing anti-albiglutide antibodies by 14 days in rodents, meaningful 2-year studies in rats or mice are not feasible. Immune compromised mice. - A dose-dependent increase in plasma calcitonin levels (male and female): potential to cause C-cell hyperplasia and thyroid tumours in rodents. - Not suitable models: early decrease in systemic exposure. **Reproduction toxicity** - Mouse embryofoetal developmental: bent ribs (high dose)	**Important identified risks** - Acute Pancreatitis - GI events - Hypoglycaemia - Injection Site Reactions - Immunogenicity - Pneumonia - Atrial fibrillation/flutter **Important potential risks** - CV safety of antidiabetic therapy - Medullary Thyroid Cancer (Thyroid C-cell Tumours nonclinical) - Hepatotoxicity - Pancreatic cancers - Intestinal Obstruction - Foetal & neonatal developmental toxicity-nonclinical - Accelerated sexual maturation (based on nonclinical) - **Missing information** - Use in pregnancy and lactation - Use in paediatric population - Use in hepatic impairment - Use in very elderly (age ≥ 75 years) - Use in severe renal impairment (eGFR < 30 ml/ by MDRD) - Use in NYHA Class III/ IV heart failure	**Important identified risks** - Acute Pancreatitis - GI events - Hypoglycaemia - Injection Site Reactions - Immunogenicity - Pneumonia - Atrial fibrillation/flutter **Important potential risks** - CV safety - Medullary Thyroid Cancer (Thyroid C-cell Tumours nonclinical) - Hepatotoxicity - Pancreatic cancers - Malignant neoplasms following combination treatment with insulin - Foetal & neonatal developmental toxicity (nonclinical) - Accelerated sexual maturation (nonclinical) - **Missing information** - Use in pregnancy and lactation - Use in paediatric population - Use in hepatic impairment - Use in very elderly (age ≥ 75 years) - Use in severe renal impairment (eGFR < 30 ml/ by MDRD) - Use in NYHA Class III/ IV heart failure

Table 17 - Summary of safety concerns considered by EMA and FDA for EPERZAN and TANZEUM, respectively.

	EMA	FDA [52] [53]
Safety concerns	**Important identified risks** - Acute Pancreatitis - GI events - Hypoglycaemia - Injection Site Reactions - Immunogenicity - Pneumonia - Atrial fibrillation/flutter **Important potential risks** - CV safety - Medullary Thyroid Cancer (Thyroid C-cell Tumours nonclinical) - Hepatotoxicity - Pancreatic cancers - Malignant neoplasms following combination treatment with insulin - Foetal and neonatal developmental toxicity (nonclinical) - Accelerated sexual maturation in juveniles (nonclinical) **Missing information** - Use in pregnancy and lactation - Use in paediatric population - Use in hepatic impairment - Use in very elderly (age ≥ 75 years) - Use in severe renal impairment (eGFR < 30 ml/ by MDRD) - Use in NYHA Class III/ IV heart failure	- Acute Pancreatitis - GI events (e.g., nausea, vomiting, diarrhoea) - Increased hypoglycaemia in combination with drugs known to cause hypoglycaemia (SU and insulin) - Injection Site Reactions, e.g., hematoma, erythema, rash, hypersensitivity. - Pneumonia - Atrial fibrillation/Atrial flutter - Medullary thyroid cancer - CV safety - Immunogenicity, e.g., clinical sequelae of antidrug antibodies, severe hypersensitivity reactions, other immune related events - Hepatotoxicity - Use in pregnancy and lactation - Use in paediatric population - Use in patients with hepatic impairment - Worsening renal function precipitated by dehydration due to product related GI adverse reactions

The post-marketing data, meaning the ADRs reported in EU and U.S., are presented in individual charts. Additionally, a comparison of adverse reactions reported both in EU and U.S., grouped by SOC, can be seen in a chart format.

- European database of suspected adverse drug reaction reports

The data herein presented was retrieved from European database adrreports.eu [36]. This website gives access to web reports on suspected ADRs by medicine or by active substance name. All data displayed in the web reports is taken from EudraVigilance, a system designed for collecting reports of ADRs occurred within and outside the EEA [36]. This includes reports received from healthcare professionals and patients, reported by national competent authorities and MAHs.

The following charts (Chart 21 and Chart 22) illustrate the number of the ADRs reported up to July 2016 to EudraVigilance, grouped by SOC and by PT, respectively.

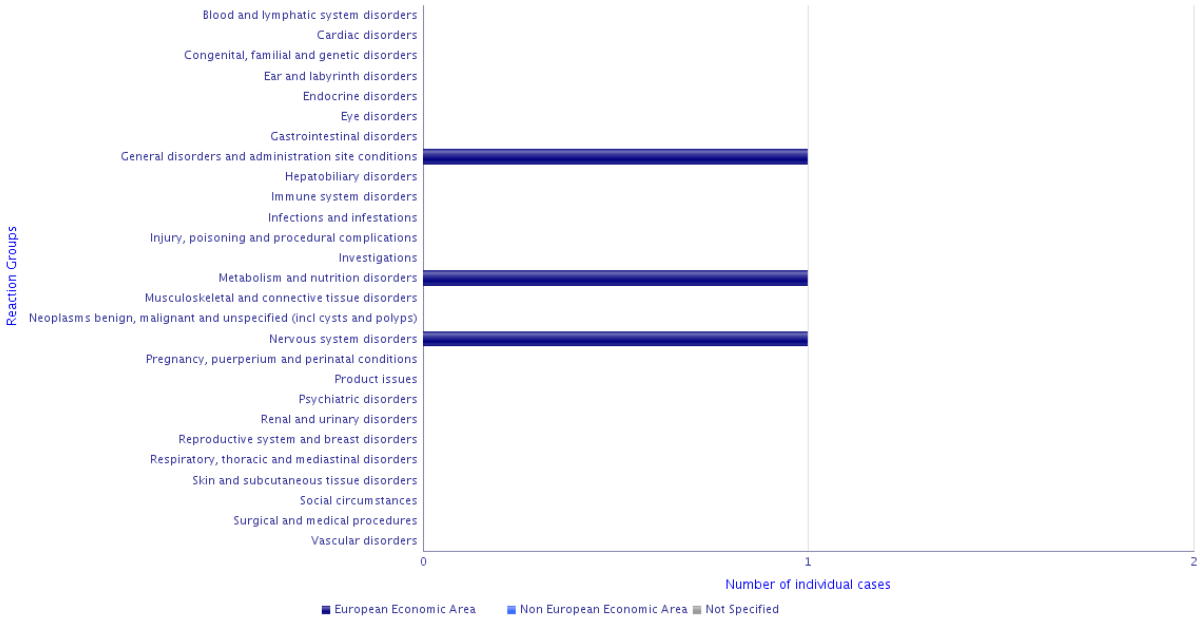

Chart 21 - Number of Individual Cases by Reaction Groups sorted by Geographic Origin in EU for EPERZAN

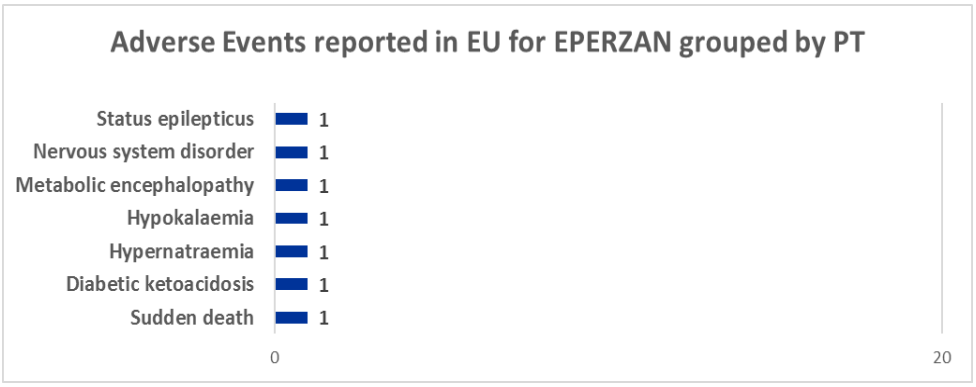

Chart 22 - Adverse Events reported in EU for EPERZAN grouped by PT

- **FDA Adverse Events Reporting System (FAERS) Data (DrugCite.com)**

This database includes information regarding the number of the ADRs reported since the authorisation date up to the Q3 2012 to FDA. As TANZEUM was only approved in 2014 in U.S., there is no data available yet.

- **Comparison of adverse events reported in EU and U.S., grouped by SOC**

As no data is available from FDA, it was not possible to perform this comparison.

It is not possible to perform a comparison between the post-marketing data in the EU and in the U.S., as no U.S. data are available. However, on the basis of the charts and tables previously presented, it is possible to perform the following analysis:

- In respect to the pre-marketing identified safety concerns, the main differences between the EU and the U.S. reside on pancreatic cancers, malignant neoplasms following combination treatment with insulin, foetal and neonatal development toxicity and accelerated sexual maturation in juveniles, which were identified in the EU as potential risks but not in the U.S..
- Regarding the safety concerns identified in the phase pre-marketing and the results obtained in the post-marketing and here presented in chart format, it is not possible to draw any analysis and/or conclusions, as the published data is not enough to enable it.

TRULICITY

TRULICITY is a new long acting human GLP-1R agonist containing dulaglutide as active substance. Dulaglutide is a disulfide-bonded covalent homodimer fusion protein encoded by a single synthetic gene. The gene for dulaglutide contains the GLP-1 analogue, linker and an engineered human immunoglobulin G4 (IgG4) heavy chain fragment (Fc) domain. This means, Dulaglutide molecule consists of 2 identical disulfide-linked chains, each containing a human GLP-1 analogue sequence covalently linked to a modified human IgG4 Fc by a small peptide linker. The GLP-1 analogue portion of dulaglutide is approximately 90% homologous to native human GLP-1 with amino acid substitutions aiming at optimizing its solubility and pharmacological activity, including protection from DPP-4 inactivation and reduced immunogenicity. The IgG-Fc increases the size of the molecule, therefore reducing the rate of clearance. The IgG4 Fc portion of the molecule was also modified to prevent half-antibody formation and to reduce the potential for interaction with high affinity Fc receptors that may result in immunologic cytotoxicity. The pharmacokinetic profile of dulaglutide suggests a plasma half-life (t1/2) of approximately 4.7 days, which makes it suitable for once weekly administration [30, 40].

Dulaglutide is a clear, colourless solution for injection and is available as a prefilled syringe (PFS) and a prefilled pen, each for single use only. Dulaglutide is available in two strengths: 0.75 mg in 0.5 ml solution, and 1.5 mg in 0.5 ml solution. For monotherapy, the recommended dose is 0.75 mg once weekly by SC injection. For add-on therapy the recommended dose is 1.5 mg once weekly [40].

These medicinal product is approved in monotherapy and in several therapeutic combinations, as identified in Table 4 - Approved therapeutic indications.

Regarding the TRULICITY' safety profile, comparative analyses are presented. A comparison between safety information included in EPAR (nonclinical and clinical data) and in RMP is illustrated in Table 18. Table 19 resumes the safety concerns considered by EMA and those ones accepted by FDA.

Table 18 - Comparative analysis on TRULICITY' safety profile

	Nonclinical data [30]	Clinical data [30]	RMP data [40]
Safety concerns	Monkey: - Ani-drug antibodies not detected - QTc prolongation observed (higher doses than the proposed clinically) **Toxicology** Rat: - No pancreatic inflammation, necrosis, hyperplasia or neoplasia (58-fold the maximum recommended human dose [MRHD]) Monkey: - No thyroid C-cell neoplasia or pancreatic inflammation, necrosis, hyperplasia, or neoplasia (474-fold the MRHD). **Carcinogenicity** Transgenic mice: - No thyroid C-cell neoplasia or pancreatic inflammation, necrosis, hyperplasia, or neoplasia (4-fold the MRHD) Rat: - Non-fatal, thyroid C-cell tumours (≥ 7-fold the MRHD). - C-cell carcinomas were noted - No pancreatic inflammation, necrosis, hyperplasia or neoplasia (58-fold the MRHD). Non-diabetic rat: - Increased focal thyroid C-cell hyperplasia (chronic treatment) - Not increase diffuse C-cell hyperplasia or basal or calcium chloride-stimulated plasma calcitonin. **Reproduction Toxicity** Rat / Rabbit - Embryofoetal development studies: skeletal effects were noted and memory deficits were observed.	**Important Identified Risks** - Hypoglycaemia - Acute pancreatitis - GI events **Important Potential Risks** - Hypersensitivity - Thyroid C-cell tumours - Pancreatic malignancy - CV effects - Medication errors (more than one injection per week) **Missing Information** - Use in children and adolescents <18 years of age - Use in pregnant and/or breastfeeding women - Use in patients with hepatic impairment - Use in patients with severe renal failure - Use in patients with congestive heart failure - Use in patients aged ≥75 years - Confirmation of memory deficits in directly dosed immature rats	**Important Identified Risks:** - Hypoglycaemia - Acute pancreatitis - GI events **Important Potential risks** - Hypersensitivity - Thyroid C-cell Tumours - Pancreatic malignancy - CV effects - Medication Errors (more than one injection per week) **Missing Information** - Use in children and adolescents <18 years of age - Use in pregnant and/or breastfeeding women - Use in patients with hepatic impairment - Use in patients with severe renal failure - Use in patients with congestive heart failure - Use in patients aged ≥75 years - Confirmation of memory deficits in directly dosed immature rats

Table 19 - Summary of safety concerns considered by EMA and FDA for TRULICITY

	EMA	FDA [54, 55]
Safety concerns	**Important Identified Risks:** - Hypoglycaemia - Acute pancreatitis - GI events **Important Potential risks** - Hypersensitivity - Thyroid C-cell Tumours - Pancreatic malignancy - CV effects - Medication Errors (more than one injection per week) **Missing Information** - Use in children and adolescents <18 years of age - Use in pregnant and/or breastfeeding women - Use in patients with hepatic impairment - Use in patients with severe renal failure - Use in patients with congestive heart failure - Use in patients aged ≥75 years - Confirmation of memory deficits in directly dosed immature rats	- Increased hypoglycaemia in combination with drugs known to cause hypoglycaemia (SU and insulin) - Acute pancreatitis - GI reactions, e.g. diarrhoea, nausea and vomiting; - Hypersensitivity reactions - Thyroid c-cell tumours, including medullary thyroid cancer - Pancreatic cancer - CV events (e.g. increased heart rate) - Immunogenicity, i.e. anti-dulaglutide antibodies - Worsening renal function precipitated by dehydration due to product related GI adverse reactions

- European database of suspected adverse drug reaction reports

The data herein presented was retrieved from European database adrreports.eu [36]. This website gives access to web reports on suspected ADRs by medicine or by active substance name. All the data displayed in the web reports is taken from EudraVigilance, a system designed for collecting reports of ADRs occurred within and outside the EEA [36]. This includes reports received from healthcare professionals and patients, reported by national competent authorities and MAHs.

The following charts (Chart 23 and Chart 24) illustrate the number of the ADRs reported for TRULICITY up to July 2016 to EudraVigilance, grouped by SOC and by PT, respectively.

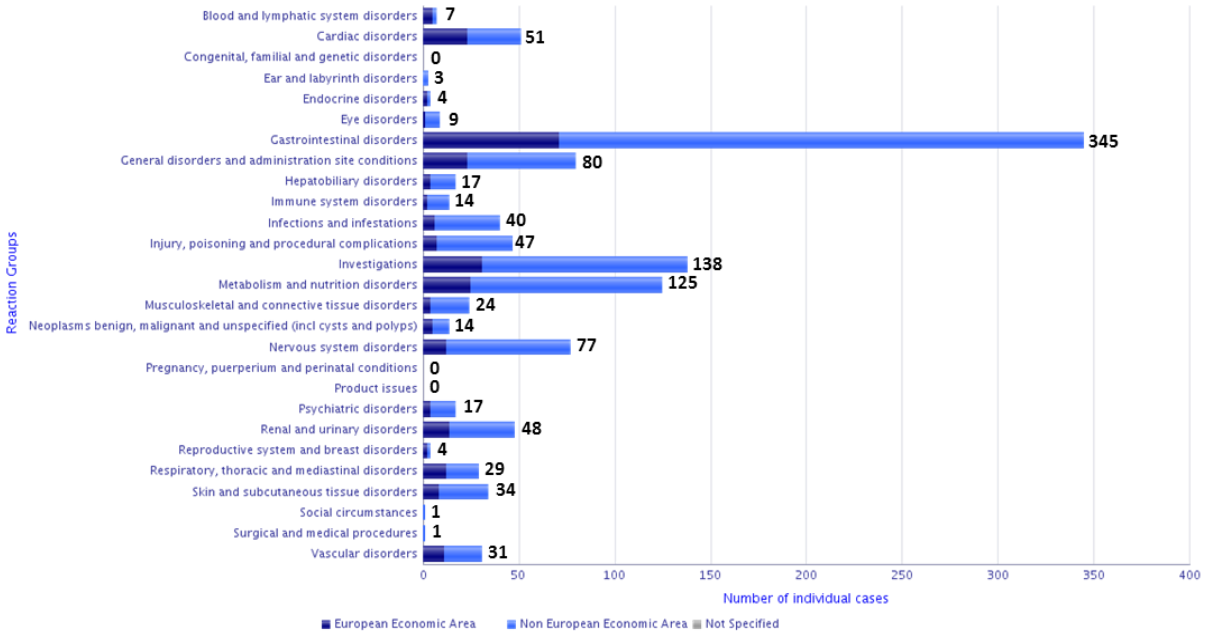

Chart 23 - Number of Individual Cases by Reaction Groups sorted by Geographic Origin in EU for TRULICITY

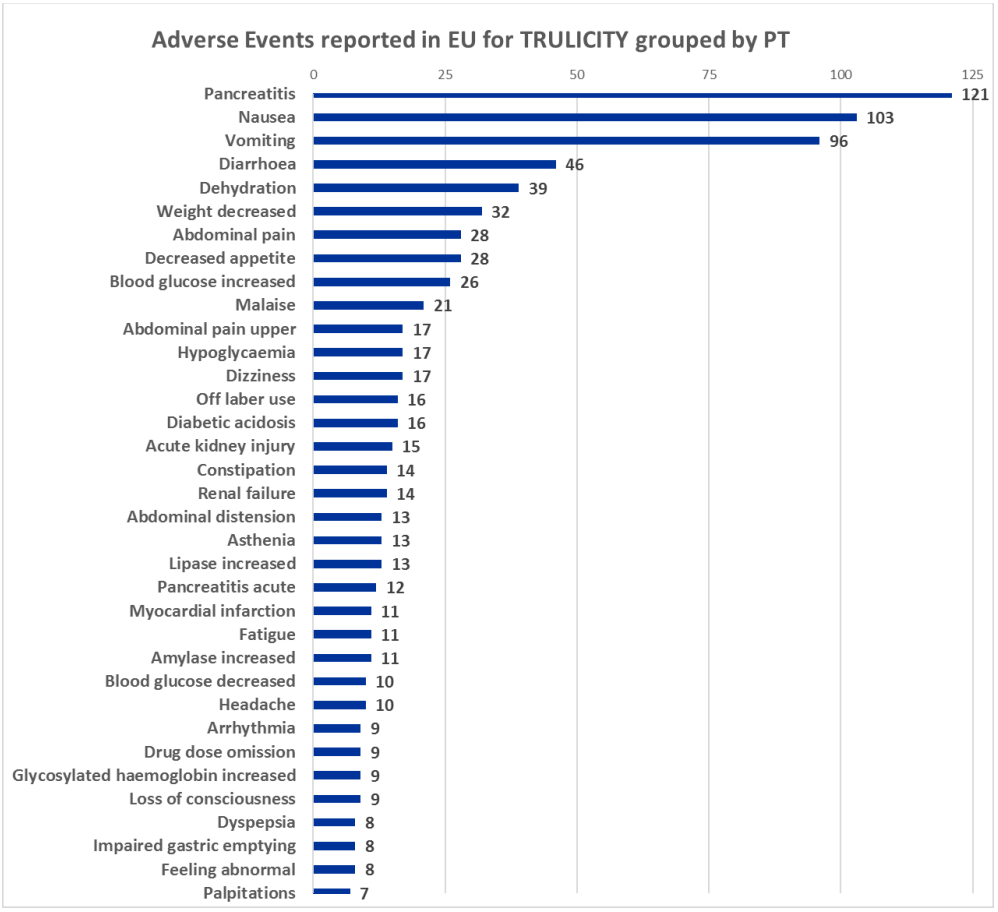

Chart 24 - Adverse Events reported in EU for TRULICITY grouped by PT

- **FDA Adverse Events Reporting System (FAERS) Data (DrugCite.com)**

This database includes information regarding the number of the ADRs reported since the authorisation date up to the Q3 2012 to FDA. As TRULICITY was only approved in 2014 in U.S., there is no data available yet.

- **Comparison of adverse events reported in EU and U.S., grouped by SOC**

As no data is available from FDA, it was not possible to perform this comparison.

It is not possible to perform a comparison between the post-marketing data in the EU and in the U.S., as no U.S. data are available. However, on the basis of the charts and tables previously presented, it is possible to perform the following analysis:

- Hypoglycaemia is considered a risk both in the EU and in the U.S.. Hypoglycaemia and blood glucose decreased have been reported in the EU.
- Acute Pancreatitis belong to the list of risks associated with the use of dulaglutide, both in the EU not in the U.S.. This risk is corroborated by the real world data, since represents the ADR most reported in the EU, with a very high prevalence.
- GI AEs, such as diarrhoea, nausea and vomiting, are identified risks associated with this medicinal product. Accordingly, *GI disorder* SOC is the SOC with the major number of cases reported in the EU, being nausea, vomiting and diarrhoea, after pancreatitis, the most reported ADRs.
- Hypersensitivity reactions were identified in the pre-marketing phase as being risks for this medicinal product both in the EU and in the U.S.. Nevertheless, by the analysis of the PT chart it is possible to realise that hypersensitivity reactions are not presented among the 35 reactions most reported. Additionally, the *SOC Immune system disorders i*s one of those with less cases reported.
- Pancreatic cancers and thyroid C-cell tumours are considered risks in the EU and in the U.S.. The SOC *Neoplasms benign, malignant and unspecified* is among those ones with less reports in the EU. Moreover, concerning the PTs charts, no carcinomas are presented in the 35 most reported reactions.
- CV events were considered potential risks for this medicinal product in the both geographical areas. The *SOC Cardiac disorders* is on the 6th position of prevalence in the EU, and what concerns to the PTs there are some cardiac reactions presented in the 35 most reported ADRs, such as myocardial infarction, arrhythmia and palpitations.
- Decreased renal function and dehydration are identified as risks in the U.S.. In accordance with the data presented in the charts, these are verified as *Renal and urinary disorders SOC* have a moderate prevalence, occupying the 7th position in the SOC chart. Also in the PT chart, dehydration is 4th reaction most reported and acute kidney injury and renal failure are presented among the top 20 of the most reported ADRs.

- Immunogenicity (anti-dulaglutide antibodies) is identified as risk in the U.S., but not in the EU. On the basis of the charts results, this is not verified in the EU post-marketing data.
- Weight decreased is not identified as risk but it 5th reaction most reported.
- Blood glucose increased not considered as a risk, it has the 9th position of the most PTs reported.
- *Nervous system disorders SOC* appears among the most prevalent SOCs, being the 5th with most prevalence.

Discussion

Despite GLP-1R agonists are authorised in Europe since 2006 (BYETTA'S approval year), in Portugal only in 2014 the first GLP-1R agonists were reimbursed. The reimbursement was approved for VICTOZA in January 2014 and for BYDUREON in October 2014. BYETTA'S reimbursement request was rejected not showing therapeutic nor economic advantage. In coming years, it is expected that several other GLP-1 agonists become reimbursed. The post-marketing experience gathered by other countries, both in Europe and U.S., is of most importance, as it enables to draw a more accurate safety profile for these medicines and allows deducing which will be the most serious adverse reactions to be expected in Portuguese patients using these medicinal products.

At an initial stage, only BYETTA, VICTOZA and BYDUREON were included in the analysis, since they were the first GLP-1R agonists approved for T2DM both in the EU and in the U.S., and for which the reimbursement had been requested in Portugal. Nevertheless, and as observed in Table 2 - GLP-1R agonists approved in EU and Table 3 - GLP-1R agonists approved in U.S., there are other three medicinal products (LYXUMIA/ADLYXIN, EPERZAN/TANZEUM and TRULICITY) approved in the EU and in the U.S.. As the main goals of the present work are drawing a safety profile for GLP-1R agonists and conclude on the need and/or opportunity of adapting the RMP for the new markets, taking into account the safety data collected both in the EU and in the U.S., include LYXUMIA/ADLYXIN, EPERZAN/TANZEUM and TRULICITY in this evaluation seem to be a real asset.

By the results presented previously, it was noticeable that there were some discrepancies, not only between the safety concerns identified in the EU and in the U.S. for the same medicinal products but also there are differences in the safety concerns identified among the several medicinal products.

Following specific analysis performed for each medicinal product, the Table 20 and Table 21 intend to present a global picture of the safety profile of the GLP-1R agonists class. The first presents all the medicinal products with their respective safety concerns identified in the pre-marketing phase and the last provides the ranking of the most prevalent SOCs for this pharmacological class. For comparison purposes, there was the need to choose a common data set and, for that reason and as no complete U.S. data is available for LYXUMIA/ADLYXIN, EPERZAN/TANZEUM and TRULICITY, both tables comprise the EU pre- and post-marketing data, respectively.

A thorough analysis of each SOC considered relevant to the present work will be also presented in this section. Moreover, whenever considered applicable, a specific safety concern may be specifically addressed in this analysis, instead of analysing the SOC in general. The concerned analysis will include all the data results presented in the RESULTS section as well as will refers to the data presented in the tables provided below.

Table 20 - Comparison of safety concerns identified for all GLP-1R agonist (pre-marketing EU data)

	Exenatide	Exenatide-extended release	Albiglutide	Dulaglutide	Liraglutide	Lixisenatide
Important Identified Risks	Pancreatitis					
			Hypoglycaemia			
	Acute Renal failure					
	Rapid Weight Loss					
			GI events (nausea, diarrhoea, vomiting, constipation and dyspepsia)			
						Hypersensitivity
			Injection Site Reactions			
			Immunogenicity			
			Pneumonia			
			Atrial fibrillation/flutter			
Important Potential Risks	Cardiovascular effects / Cardiac co-morbidity					
				Hypersensitivity / Immunogenicity (antibodies)		
	Thyroid Neoplasms					
	Pancreatic cancers					
					Pancreatitis (acute)	
	Malignant Neoplasms				Malignant Neoplasms	
			Hepatotoxicity			
			Foetal & neonatal developmental toxicity			Teratogenicity
				Medication Errors		
					Late stage microvascular eye complication	
						Dehydration
						Acute renal impairment
						Off-label use (weight loss)
Missing Information	Use in children and adolescents <18 years of age					
	Use in pregnancy and/or lactation					
	Use in very elderly (age ≥ 75 years)					
	Potential for Concomitant use with TZDs					
		Use in patients with moderate and severe renal impairment				
		Use in patients with hepatic impairment				
		Severe GI disease				
			Use in patients with congestive heart failure			
				Memory deficits (rats)		
					Overdose	
					Abuse due to weight lowering potential	
					Drug-drug interaction with warfarin	
					Off-label use	

Table 21 - Comparison of most prevalent SOCs for all GLP-1R agonist (post-marketing EU data)

MedDRA 19.0 System Organ Class (SOC)	Post-Marketing EU data – rating of AEs mostly reported					
	BYETTA	BYUDUREON	VICTOZA	LYXUMIA	TRULICITY	EPERZAN
Cardiac disorders	11th	11th	9th	10th	6th	-
Gastrointestinal disorders	1st	1st	1st	1st	1st	-
General disorders and administration site conditions	4th	2nd	4th	3rd	4th	1st
Hepatobiliary disorders	10th	18th	8th	13th	14th	-
Immune system disorders	20th	14th	19th	12th	16th	-
Infections and infestations	9th	8th	10th	7th	9th	-
Injury, poisoning and procedural complications	5th	4th	11th	8th	8th	-
Investigations	2nd	3rd	3rd	4th	2nd	-
Metabolism and nutrition disorders	6th	6th	5th	2nd	3rd	1st
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3rd	9th	2nd	17th	17th	-
Nervous system disorders	8th	5th	6th	5th	5th	1st
Renal and urinary disorders	7th	13th	7th	9th	7th	-
Respiratory, thoracic and mediastinal disorders	12th	10th	13th	11th	12th	-
Skin and subcutaneous tissue disorders	14th	7th	12th	6th	10th	-

*Note: The colours represent the ranking of reported AEs. **RED** represents the mostly reported and **GREEN** the least reported AEs.*

As observed in the table above, for EPERZAN there is no relevant data in the post-marketing environment. Therefore, in the analysis presented below, associated with the post-marketing data, whenever "all medicinal products" are referred this medicinal product is not included.

CARDIAC DISORDERS SOC

Patients with T2DM have a several-fold increased risk of developing CV disease when compared with nondiabetic controls [56]. GLP-1R was detected in cardiac and vascular tissues and GLP-1R protein was also detected in human coronary artery endothelial cells and human umbilical vein endothelial cells [56]. The effect of GLP-1R agonists on heart failure remains uncertain [57]. Animal studies have shown that the GLP-1R agonist liraglutide can activate cytoprotective pathways in the heart, and improve outcomes after experimental myocardial infarction in mice. Early clinical studies also suggested that GLP-1R agonists have positive effects on CV biomarkers, such as high-sensitivity C-reactive protein and plasminogen activator inhibitor-1, and improve regional and overall left ventricular function in patients with acute myocardial infarction and severe systolic dysfunction after successful

primary angioplasty [57]. *Li L, et al* [57], based on their findings, concluded that the current evidence suggests that GLP-1R agonists do not increase the risk of heart failure or hospitalization for heart failure. The current body of evidence, however, is not definitive.

An increase in heart rate, independent risk factor for cardiac mortality, accompanied by a decrease in blood pressure has been reported during treatment with liraglutide and exenatide. The mechanism behind the change in heart rate is not known, but might involve increased natriuresis and lowered blood pressure. Whether the benefit of the decrease in blood pressure outweighs the harm of the increase in heart rate remains to be determined. Several large CV outcome trials (LEADER (liraglutide), EXSCEL (exenatide once-weekly), ELIXA (lixisenatide), REWIND (dulaglutide)) including up to 9,500 patients with T2DM are ongoing and are expected to be completed between 2016 and 2019 [58]. When the results from these trials are available, there will be more definitive answers on the relationship between GLP-1R agonists and CV safety [59, 60].

Regarding Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) study, American Diabetes Association stated that no increased risk for CV death, heart attack, stroke, unstable angina or heart failure was found in people with T2DM who had recently experienced acute coronary syndrome events and were therefore at high risk for additional heart problems. The study examined 6,068 people from 49 countries, randomly assigning them to lixisenatide or placebo, with a follow-up period of more than two years [61].

A recent press release for the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial investigating the CV safety of the GLP-1R agonist, stated that liraglutide reports reduced CV risk assessed by the composite outcome of the first occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke [62].

Overall, GLP-1R agonists have demonstrated positive CV outcomes with slight improvements in blood pressure and lipid parameters and modest improvements in weight. According to Prasad-Reddy L. *et al,* a meta-analysis of 33 trials consisting of exenatide twice daily, exenatide weekly, liraglutide, and albiglutide showed no increase in major CV events, including myocardial infarctions, strokes, and all-cause mortality, when compared to other agents or placebo. Thus far, studies and post-marketing reports with exenatide and liraglutide have not demonstrated any prolongation of the QT interval [59].

On the basis of the data presented in the previous section, CV effects or cardiac co-morbidity were identified in the EU during the pre-marketing phase as potential risks for all the medicinal products under analysis. Additionally, atrial fibrillation and atrial flutter were also classified as important identified risks for EPERZAN.

Referring to the U.S., the CV events were also considered safety risks associated with the use of these medicinal products, excepting for BYETTA and for ADLYXIN. Similar to the EU, for EPERZAN atrial fibrillation and atrial flutter were also considered risks.

Regarding the real-world data, is possible to realize that for the majority of the medicinal products the *Cardiac disorders* SOC is not one of the most prevalent. Nevertheless, for BYDUREON and TRULICITY, in the U.S. and in the EU respectively, this SOC occupies the

6th position in the ranking of the most prevalent, being myocardial infarction, palpitations, atrial fibrillation and arrhythmia among the 35th most reported PTs.

According to the aforementioned information, it is possible to conclude that the CV risk is not fully clarified nor completely linked to the GLP-1R agonist class. Therefore, and taking into account all the minimisation measures implemented for all the medicinal products concerned, CV risks should be continuously considered as important potential risks associated with this therapeutic class.
Large multicentered studies are currently underway, to confirm the CV safety use of incretins in subjects with T2DM. These studies will allow to get a better understanding on CV effects of the GLP-1R agonists.

GASTROINTESTINAL DISORDERS SOC

In the EU, GI events, such as nausea, diarrhoea and vomiting, were included in the important identified risks for all medicinal products except for the exenatide-containing medicines, BYETTA and BYDUREON. Severe GI disease was considered missing information related to the use of BYDUREON. In the U.S., these events were also associated with the use of the all GLP-1R agonists class.

The PT pancreatitis also belongs to the *GI disorders* SOC. This ADR is classified as important identified risk to the BYETTA, BYDUREON, EPERZAN and TRULICITY, and it was considered potential risk for VICTOZA and LYXUMIA, in the EU. Concerning the U.S., pancreatitis was identified as risk for all GLP-1R agonists, except for BYETTA.

Clinical trials with GLP-1R agonists have reported the most frequently reported treatment-related AE about GLP-1 RAs was GI disorders, mainly nausea, vomiting, and diarrhoea. Some research has shown that the GI AEs associated with GLP-1 RAs are dose dependent and decline over time [63-65]. Delayed gastric emptying will lead to gastrointestinal symptoms, such as early satiety, postprandial fullness, epigastric pain, nausea, and vomiting. Although these GI symptoms are not considered to be important causes of mortality in T2DM, they have obvious negative influences on diabetes control, diabetes complications, and health-related quality of life [58, 59, 63].

The incidence of acute pancreatitis is increased in the background T2DM population, possibly because of the coexistence of occult exocrine pancreatic abnormalities in the diabetic population, or possibly because of a high prevalence of obesity and gallstones. Most studies have not confirmed an increased incidence of acute pancreatitis with GLP-1R agonist therapy, but these lacked the statistical power to exclude a smaller effect (e.g. up to 2-fold increase) [58, 64, 65].

When exenatide twice daily first became available, there was reporting of exenatide-induced pancreatitis. This led the FDA to release a warning referring that post-marketing studies of exenatide may suggest a link between treatment and acute pancreatitis, and that healthcare professionals should monitor for signs of pancreatitis in patients using these agents [59].

Over time, several assessments of pancreatitis-related to GLP-1R agonists have been performed by EMA. In 2013, EMA was made aware of findings by a group of academic researchers suggesting an increased risk of pancreatitis and cellular changes in patients treated for T2DM with GLP-1 based therapies. The investigators described a number of findings in the pancreata of the T2DM individuals treated with these medicines which could implicate an association of the treatment with increased risk of pancreatitis and neoplasms [66].
A significant number of cases were observed and a causal relationship between GLP-1 based therapy treatment and pancreatitis was considered possible. Warnings were already included in the product information for all products, albeit with small differences in the wording, and pancreatitis was being followed in the periodic safety update reports as well as in observational and randomised clinical trials. Therefore, EMA concluded that these actions were sufficient and no new data had emerged that implies that this risk is higher compared to what had previously been concluded. However, with the next updates of the RMPs, pancreatitis, which should be already mentioned in the RMPs as a potential risk should be listed as an identified risk for all products and it would be appropriate to harmonize the wording of the warning with respect to a recommendation to use the products with caution in patients with a history of pancreatitis as well as a recommendation not to resume treatment if pancreatitis has occurred [66]. In conclusion, according to Pharmacovigilance Risk Assessment Committee (PRAC) recommendation, the results of the study by *Butler et al* were not considered to constitute a new safety signal for the GLP 1 based therapies with respect to pancreatic safety. This was further supported by the review of available preclinical and clinical data. However, due to the mechanism of action, there were still some uncertainties with respect to long term pancreatic safety associated with these products and updates to the RMPs (including planned and ongoing studies) and harmonisation of warnings in the product information were taken forward [66].

In the post-marketing presented in the previous section, *GI disorders* is the mostly reported SOC in all medicinal products (1st place in the ranking).

Regarding nausea, diarrhoea and vomiting it is easily observed that these adverse reactions belong to the top 10 of the mostly reported for almost all the medicinal products either in the EU or in the U.S.. A single difference remains in BYDUREON, in the U.S., for which vomiting is not included in the top 10 but it occupies the 19th position.

Concerning pancreatitis, by the analysing of the PT charts of each medicinal product, it is observed that for BYETTA, VICTOZA and TRULICITY this adverse reaction appears as the mostly reported (1st position), as per the EU data. BYDUREON also presents a high rate of pancreatitis once it appears in the 2nd position of the mostly reported. LYXUMIA is the medicinal product with less prevalence of this adverse reaction, in which this reaction has the 13th place of the ranking. Other forms of pancreatitis are also reported, such as pancreatitis acute or chronic. It seems important to highlight the occurrence of pancreatitis associated with VICTOZA, as pancreatitis occupies the 1st place in the mostly reported chart and pancreatitis acute has the 3rd one. This medicinal product presents the high prevalence of pancreatitis among all the GLP-1R agonists class.
When comparing the data obtained in the EU and that in the U.S., it is realized that in the U.S. the prevalence of occurrence such adverse reaction is lower than in the EU.

According to the aforementioned information, it is possible to conclude that the GI events, such as nausea, vomiting and diarrhoea, are directly linked to the use of the GLP-1R agonists, as they were identified and prevalent for all medicines in this therapeutic class.
Pancreatitis is also a safety concern linked to the utilisation of these medicinal products having a high prevalence in all the medicinal products mainly with VICTOZA. Hence, this safety concern should be considered a class effect and should be classified as important identified risk for all GLP1-R agonists.

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS SOC

This concerned SOC comprises several adverse reactions affecting patient's general well-being, such as malaise, asthenia, fatigue and pain, as well as adverse reactions associated with the drug administration site.

These kind of reactions were not identified as risk for all the medicinal products. In the EU, injection site reactions were only considered as potential risk for VICTOZA and were classified as important identified risk for EPERZAN.

Regarding the U.S., injection site nodules and reactions were identified as risk for BYDUREON and injection site reactions were also considered risks for VICTOZA and TANZEUM.

In the literature it was also found some data identifying that injection-site reactions were more common with the once weekly formulation, which is expected, as symptoms, particularly itching, have been shown to have a higher incidence with injectable sustained-release products that degrade over time in the body [60]. Exenatide once weekly had higher reporting of injection site reactions, including nodule formation after injection [60]. Injection-site reactions may be more common with the longer acting agents, particularly exenatide once weekly which can cause transient small nodules at the injection site. However, patient satisfaction data indicate that once weekly injections result in higher patient satisfaction compared with twice daily injections[65].

According to Table 21 presented at the beginning of this section, *General disorders and administration site conditions* SOC is the 3rd with most prevalence, being in the 2nd place of the ranking for BYDUREON, the 3rd for LYXUMIA and the 4th for the remaining medicinal products.

Based on the data available regarding the top 35 of adverse reactions reported in the global population, general disorders, for instance malaise, asthenia and fatigue, are presented in this top in general for all medicinal products, both in the EU and in the U.S., whenever applicable.

As BYETTA and BYDUREON have the same active substance, it was expected that both of them had a similar safety profile. Still, it is not verified as some slight differences are observed either in Chart 11 or in Chart 12 and Chart 13. One example of these discrepancies

is the prevalence of this concerned SOC, once it is more prevalent with BYDUREON than with BYETTA. According to data displayed in Chart 13 it is possible to realize that BYDUREON presents much more reports of site administration reactions than BYETTA.

Therefore, the pre-marketing data is in accordance with the post-marketing data presented throughout this work, and these findings are in agreement with the scientific information published in the literature.

IMMUNE SYSTEM DISORDERS SOC

Hypersensitivity reactions, most of times as anaphylactic-type reactions, and immunogenicity were associated with all the medicinal products under analysis. The occurrence of such reactions was closely linked to the occurrence of anti-drug antibodies.

In the EU, on one hand, immunogenicity was classified as important potential risks for all medicines, excepting for EPERZAN, for which these reactions were considered important identified risks, and for TRULICITY, for which this reaction was not included in the risks. On the other hand, hypersensitivity was considered important potential risks for all except LYXUMIA and for EPERZAN, for which this reaction was included in the important identified risks and was not included in the risks, respectively.

Concerning the U.S., both immunogenicity and hypersensitivity reactions were linked to all the medicinal products, being identified as risks for all of them.

GLP-1R agonists are therapeutic peptides and, therefore, there is concern that antidrug antibodies could develop leading to decreased efficacy or to local or systemic hypersensitivity and neutralization over time [58, 59, 65, 67]. Antibody levels have been measured in clinical trials, with significant variation between the various GLP-1R agonists, which is thought to be due to differences in immunogenicity of the formulations. Newer formulations, including albiglutide and dulaglutide, have less risk of antibody formation compared to exenatide and liraglutide [59, 65, 67]. Exenatide produces the most antibodies out of the marketed GLP-1R agonists, possibly due to the lower sequence identity of exenatide with native GLP-1. Among the two exenatide formulations, exenatide weekly produces more antibodies than exenatide twice daily. Higher rates of injection-site reactions were observed in patients with antibody-positive titers, but other adverse effects were not statistically different. Those with high antibody titers overall had a smaller improvement in hemoglobin A1C values; however, there was no correlation found in hemoglobin A1C values between patients with negative titers versus those with low titers. [58, 59]

Table 21 shows that *Immune system disorders SOC* is not one of the mostly prevalent for none of the medicines. Nonetheless, LYXUMIA appears has being the one with the higher prevalence, followed by BYDUREON.

The data available in the U.S. is in accordance with the results presented in the EU. The comparative charts of adverse events reported in the EU and in the U.S. grouped by SOC (Chart 5, Chart 10 and Chart 18) show that the prevalence of this SOC in the U.S. is similarly low.

Even though parenteral administration of GLP-1R agonists may trigger an immune response, the available post-marketing data shows that such adverse reactions in the general population, compared to other safety concerns, have not a high prevalence. Therefore, it is possible to conclude that this safety concern is adequately addressed for all medicinal products.

INVESTIGATIONS SOC

In this SOC are included only PTs representing investigation procedures and qualitative results. Therefore, the most relevant PTs under analysis in this SOC are weight decreased and blood glucose increased.

As seen in Table 21, *Investigations* SOC is the 2nd most prevalent for this therapeutic class.

- **Weight decreased**

Despite having been observed in all the medicines, weight loss was an important identified risk considered only for BYETTA and BYDUREON, in the EU. At some point of the time, this effect had turned up into a beneficial outcome associated with the use of GLP-1R agonists. Thus, for VICTOZA and LYXUMIA the abuse due to weight lowering potential and off-label use for weight loss were addressed as missing information and important potential risk, respectively.

In the U.S., no safety concerns related to weight loss due to use of this medicines were considered.

GLP-1 decreases GI motility, which increases the time that nutrients can be absorbed. It also increases satiety, increases resting metabolic rate, and lowers plasma concentrations of free fatty acids. In patients with T2DM, GLP-1 is diminished. In a meta-analysis that included 21 trials and 3395 participants randomly assigned to GLP-1R agonists compared with 3016 participants in various different control groups of different diabetes treatment agents, all trials showed a reduction in weight, which ranged from –0.2 to –7.2 kg. Higher doses of GLP-1R agonists correlated with greater weight loss [59].

It is hypothesized that the mechanism by which GLP-1R agonists induce weight loss might be related to multiple actions involving the brain and gastrointestinal tract, as suppressed appetite, reduced body fat, and improved endothelial function. Liraglutide is the first GLP-1R agonist specifically approved for weight loss in patients without a history of T2DM, with the brand name Saxenda® [59, 65, 68].

Besides its presence in the GI tract, GLP-1 is found in the central nervous system localized to neurons primarily in the nucleus of the solitary tract in the caudal brainstem. Neurons in the nucleus of the solitary tract that express GLP-1 send projections to several brain regions that take part in feeding behaviour and energy homeostasis. Thus, GLP-1R antagonists show broad metabolic effects, far beyond the glycaemic control, and represent effective therapies for T2DM [65].

According to the post-marketing data analysed during this work, both in the EU and in the U.S., BYETTA and BYDUREON presented weight decreased as one of the mostly reported ADRs, as for BYETTA this reaction occupied the 2nd place in both areas and for BYDUREON it was in the 3rd and in the 2nd position in the EU and in the U.S., respectively. VICTOZA and TRULICITY also presented a higher prevalence for this PT, being in the 7th and 6th positions, respectively, in the EU. In the U.S. VICTOZA also presented this PT in the 5th position of the mostly reported adverse events. LYXUMIA, among all the medicines, is the one which presents a lower prevalence for weight decrease (26th position).

GLP-1R agonists have been associated with significant weight loss in patients with diabetes, and a question of whether these agents could be used for weight loss in patients without diabetes was raised [68]. As previously stated, liraglutide is already approved for weight loss in patients without T2DM. Per the clinical and non-clinical data as well as per the post-marketing information herein presented, GLP-1R agonists are effective in this condition and so the using of these medicinal products out of the approved indications may be a possibility. Therefore, off-label use for weight loss should be an important potential risk for all these medicines.

- **Blood glucose increased**

One of the most frustrating things that diabetics deal with is an unexpected rise in blood glucose overnight. Morning hyperglycaemia in diabetic subjects may be caused by the Dawn Phenomenon or the Somogyi Effect [69].

The Dawn Phenomenon is a condition described in patients with diabetes mellitus that is characterized by abrupt increases in fasting levels of plasma glucose or insulin requirements or both, in the absence of antecedent hypoglycaemia [70]. According to *Sheehan J,* the pathogenesis of the Dawn Phenomenon may be tied to an exacerbation of the normal circadian variation in hepatic sensitivity to insulin observed in subjects without diabetes. Research suggests that this decrease in sensitivity is induced by the nocturnal secretion of growth hormone [71].

The Somogyi effect postulates that nocturnal hypoglycaemia causes fasting hyperglycaemia attributable to counterregulatory hormone release, namely glucagon, epinephrine, norepinephrine, growth hormone and cortisol [72, 73]. Bolli G *et al*, demonstrated that hypoglycaemia can cause rebound hyperglycaemia in the absence of the waning of insulin action and that this results primarily from an excessive increase in glucose production due to activation of glucose counterregulation by the antecedent hypoglycaemia. The concomitant waning of the effect of insulin, when it occurs, exacerbates posthypoglycaemic hyperglycaemia and increases the rapidity of its development [74]. The increase in counterregulatory hormones causes rapid mobilization of glucose from the liver and reduced insulin sensitivity decreasing peripheral tissue uptake of glucose. Because individuals with diabetes cannot counterbalance this glucose increase with endogenous insulin, rebound hyperglycaemia results [71].

The GLP-1R agonists are medicinal products with antidiabetic characteristics, so it was not expected that they lead to blood glucose increased, and so it was not addressed as a safety concern for these medicinal products.

However, per the observed in the charts presented for each medicinal product in previous section (RESULTS), blood glucose increased was the mostly reported ADR linked to the use of GLP-1R agonists. For BYETTA and BYDUREON presented positions of 5th and 1st in the EU and in the U.S., respectively. For VICTOZA this PT in the EU occupied the 10th place and in the U.S. was in the 2nd one. LYXUMIA and TRULICITY presented slight lower prevalence with this PT in 11th and 9th positions respectively.

By the aforementioned, the Somogyi effect could be the most possible cause of the hyperglycaemic ADRs reported, as these medicinal products are glucagon-based and this hormone is one of those which are involved in the Somogyi effect.

METABOLISM AND NUTRITION DISORDERS SOC

In this SOC the most relevant PTs under analysis are hypoglycaemia and dehydration.

As seen in Table 21, *Investigations* SOC is the 4th most prevalent for this therapeutic class.

- **Hypoglycaemia**

In the EU, hypoglycaemia was considered an important identified risk for all the medicinal product apart from the exenatide-containing medicinal products (BYETTA and BYDUREON). This effect was linked to the use of GLP-1R agonists concomitantly with a SU or basal insulin, which are medicines known to cause hypoglycaemia.

Similarly, in the U.S. hypoglycaemia when used together with a SU or basal insulin was also described as a safety concern for all GLP-1R agonists.

One of the advantages of GLP-1 agonist administration is that insulin secretion is glucose-dependent, and is inhibited at low glucose levels. This is an important safety feature since it means that, in contrast to injected insulin or sulfonylureas, insulin is no longer produced at low glucose levels. Use of the GLP-1 agonists in combination therapy may however aggravate the hypoglycaemic potential of the partner therapy [58]. The risk of hypoglycaemia is low with GLP-1R agonists and rates were similar across all GLP-1R agonists treatment groups, although the risk was increased with concomitant SU or insulin therapy [60, 64, 65].

Regarding real world data, by the observation of the previous charts, in the EU this ADR was presented in the top 20 in all the medicinal products. However, this prevalence was not corroborated by data from the U.S..

LYXUMIA, among all the other GLP-1R agonists, is the one which presents a higher prevalence of occurrence of this PT as it appears in the 3rd position of the mostly reported

ADRs, according to the data retrieved from the *European database of suspected adverse drug reaction reports website* [36].

As identified in the pre-marketing phase, including nonclinical studies, hypoglycaemia may occur when these medicinal products are administered concomitantly with SU or insulin.

- **Dehydration**

Dehydration, in the EU, is a safety concern only addressed for LYXUMIA as important potential risk. Referring to the U.S., dehydration due to product related GI adverse reactions was included in the safety concerns for TANZEUM and TRULICITY.

Patients with type 2 diabetes have an elevated risk for dehydration due to high glucose levels, and an increasingly popular class of diabetes drugs may increase this risk even more. Delayed gastric emptying can cause discomfort, nausea and vomiting; diarrhoea may also occur. Although these effects tend to diminish with time, and most patients find them tolerable, severe vomiting with dehydration may occur and precipitate pre-existing circulatory or renal disorders [58]. Many case reports of acute renal failure have been reported with the use of GLP-1 agonists, most likely triggered by dehydration from the gastrointestinal adverse effects—interpret vomiting and diarrhoea. Thus, it is recommended the cautious use of this drug class in patients with chronic kidney disease [65].

This ADR is presented in the top 35 of the most reported ADRs for all the medicines, except for LYXUMIA, in the EU and for VICTOZA in the U.S.. It is important to emphasise the prevalence of such reaction for VICTOZA and TRULICITY in the EU, for which dehydration occupies the 8th and the 5th position, respectively, in the ranking of the most reported PTs.

As explained, dehydration is closely linked to the GI effects, namely vomiting and diarrhoea. As these are the most recognized effects associated with these medicines, dehydration occurs in patients with moderate prevalence. Additionally, the occurrence of dehydration might lead to a worsening in the renal function. Since this PT appears in the top 35 of the mostly reported ADRs for all medicines, and once this is not considered a risk for all medicinal products, maybe an harmonisation should be performed in order to include this risk in the RMPs of the medicinal products for which it is not stated.

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) SOC

This SOC is classified anatomically, with pathologic sub-classifications for staging of both benign and malignant neoplasms.

In the EU (Medullary) Thyroid Neoplasms were addressed as important potential risk associated with the use of all medicinal products. Moreover, pancreatic cancers were also considered important potential risks for BYETTA, BYDUREON, EPERZAN and TRULICITY. Other malignant neoplasms were also classified as important potential risks for all medicinal products but TRULICITY.

Also, in the U.S. the malignancy risk was considered to the use of these medicinal products. The increased risk of medullary thyroid tumours associated with the use of GLP-1R agonists was identified for all the medicinal products excepting BYETTA. The pancreatic cancer was identified as risk for VICTOZA and TRULICITY; and other malignancies dose-related or not were addressed as safety concern for VICTOZA and LYXUMIA.

As pancreatic cancer and thyroid neoplasms were the two major concerns regarding this SOC, the following analysis will be based on them.

- **Pancreatic cancer**

GLP-1R are abundantly expressed in the exocrine pancreas, and increased pancreatic weight has been observed, consistent with a trophic effect upon duct cells. A model has been proposed whereby proliferation of duct cells leads to localized duct occlusion and low-grade pancreatic inflammation, more typically manifest by subclinical increases in pancreatic enzymes, and more rarely in severe acute pancreatitis. The model further proposes that low grade inflammation and high levels of GLP-1 activity will predispose to the development of pancreatic cancer. Precancerous changes known as pancreatic intraepithelial neoplasia lesions precede the onset of pancreatic cancer, and are frequently present in the pancreas of middle-aged and elderly people and both pancreatic intraepithelial neoplasia lesions and pancreatic adenocarcinoma may carry the GLP-1R [58].

Moreover, pancreatitis presumably acts as a risk factor for subsequent pancreatic cancer through the mechanisms of chronic inflammation and increased cell turnover, it is not surprising that there is a progressive increased risk with years of exposure. For example, in patients with inherited chronic pancreatitis, the risk increases progressively with years of exposure, eventually reaching almost 75% [75, 76]. Once chronic pancreatitis has been established, chronic inflammation and enhanced intraductal pressure due to stenosis of the pancreatic duct(s) may lead to the development of pancreatic carcinoma. While this sequence is established in the case of chronic pancreatitis, it is not as certain whether an episode of acute pancreatitis will have the same consequences. The histological hallmarks of developing pancreatic carcinoma after chronic pancreatitis are pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasms, and so-called pancreatic duct glands. The episodes of pancreatitis associated with GLP-1R agonist treatment seem to be episodes of acute pancreatitis [76].

As previously stated, in 2013, EMA was made aware of findings by a group of academic researchers suggesting an increased risk of pancreatitis and cellular changes in patients treated for T2DM with GLP-1 based therapies. The investigators described a number of findings in the pancreata of the T2DM individuals treated with these medicines which could implicated an association of the treatment with increased risk of pancreatitis and neoplasms [66]. Concerning pancreatic cancer, it was described that, in clinical trials, only single cases had been reported for some products and the duration of exposure was in the majority of the cases too short to support a causal relationship or to draw firm conclusions. The data available from clinical trials did not indicate an increased risk for pancreatic cancer with these medicines. In the post-marketing setting, cases of pancreatic cancer had been reported for most products, but in a rather large number of cases there were confounding factors or, in general, too short exposure to suspect a causal relationship with the products. It was noted

that MAHs were closely monitoring for effects on the pancreas. Long term consequences of stimulation of beta-cells and suppression of alpha cells as well as possible effects on exocrine pancreas were largely unknown and therefore some uncertainties existed. Considering that pancreatic cancers were very rare, large populations would need to be studied for a substantial duration to detect a possible increased risk. Observational studies had until that moment not been able to detect enough cases probably due to the rarity of the condition and, at least in Europe, rather low uptake of the products. Based on the above, the EMA concluded that pancreatic cancer must be included as a potential risk for all products for which it is not already reflected in the RMPs. Considering the low incidence of pancreatic cancer, results from the ongoing observational studies will also be of importance and therefore MAHs should ensure that pancreatic safety was adequately captured in these studies. Additionally, should new evidence indicate an increased risk of pancreatic cancer and/or a higher risk of pancreatitis compared to current estimations (e.g. from clinical studies and periodic safety update reports), the benefit-risk balance of GLP-1 based therapies should be re-evaluated [66].

- **Thyroid neoplasms**

GLP-1R are expressed in thyroid tissue, especially in C cells. Exposure to long-acting GLP-1R agonists has demonstrated an increase in thyroid C-cell hyperplasia, adenomas, and medullary thyroid carcinomas in mice, although not in humans. Rodent C-cells have considerably more GLP-1R than humans, which may explain the increase in some animal studies. Mice also develop thyroid C-cell carcinomas at much higher rates than humans, and increases have been observed even in mice treated with placebo. In general, medullary thyroid carcinoma in humans is very rare. Despite some reports have been identified for GLP-1R agonists, these cases are not sufficient to establish or to deny a causal association. [58, 59, 65].

The signal of medullary thyroid cancer linked to long acting GLP-1R agonists (BYDUREON, VICTOZA, EPERZAN and TRULICITY) was evaluated by PRAC in 2015 [77]. Following labelling changes in the U.S. for long acting GLP-1R agonists (liraglutide, exenatide extended-release, albiglutide, and dulaglutide) to describe the first reported human cases of medullary thyroid cancer, a signal of medullary thyroid cancer was identified by the EMA during routine signal detection activities, based on 18 cases (including 16 for liraglutide only) retrieved from EudraVigilance. The PRAC discussed and concluded that medullary thyroid carcinoma is a potential risk in the RMP of long acting GLP-1R agonists and this safety concern is addressed in several ongoing studies. It was noted that the majority of cases were reported with liraglutide - including five cases in patients without a medical history of thyroid disorder or a family history of thyroid diseases, and that non-lethal thyroid C-cell tumours had been observed in the carcinogenicity studies. The PRAC agreed to request the MAH for liraglutide-containing products to provide a cumulative review of all cases concerning medullary thyroid cancer, both from clinical trials and spontaneously reported with liraglutide. Additionally, the MAH for VICTOZA should submit to the EMA a cumulative review of all cases of medullary thyroid cancer, both from clinical trials and spontaneous source reported with liraglutide-containing products. With this cumulative review, the MAH should also provide a discussion of relevant non-clinical data and scientific literature [77]. The MAH for VICTOZA replied to the request for information on the signal of medullary thyroid cancer.

Taking into account all the available evidence from post-marketing case reports, clinical trials, non-clinical data and the literature, the PRAC agreed that currently there is insufficient evidence to confirm a causal relationship between medullary thyroid cancer and liraglutide. Although non-clinical data suggested a mechanism for an increased risk of medullary thyroid cancer after liraglutide exposure, the available data in human use provides insufficient evidence to designate this as an identified risk. Because a causal relationship couldn't be established, the PRAC considered that the current warning on thyroid cancers and the non-clinical information with regard to observations in animals sufficiently reflect the currently available data regarding medullary thyroid cancer. Medullary thyroid cancer is already a potential risk in the RMP and should be continuously monitored and new relevant cases of medullary thyroid cancer should be presented and assessed in future PSURs for liraglutide [78].

- **Overall remarks referring to "real-world" data**

Referring to Table 20, of the present work, it is possible to realize that there are some discrepancies in the prevalence of this SOC between the oldest and the most recent medicines. For BYETTA and VICTOZA, which were the first GLP-1R agonists to hit the market, the SOC *Neoplasms benign, malignant and unspecified* occupies the 3rd and 2nd positions, respectively, in the ranking of the most prevalent SOCs. Otherwise, for LYXUMIA and TRULICITY this SOC occupies the 17th position of the ranking. This fact may be due to the long stay in the market of the firsts comparing to the last ones.

It is interesting to observe what happens to this SOC in the Chart 11, which compares the prevalence of the SOCs of BYETTA and BYDUREON. As BYDUREON has been authorised several years after BYETTA this may influence the prevalence of occurrence of some ADRs (namely neoplasms). In the concerned chart, it is possible to see that the prevalence of *Neoplasms benign, malignant and unspecified* SOC is much lower with BYDUREON than with BYETTA.

By the observation of the comparison charts of ADRs reported in the EU and in the U.S. (Chart 5, Chart 10 and Chart 18) it is possible to conclude that the prevalence of this concerned SOC is much higher in the EU than in the U.S., for that medicinal products. This is specially highlighted in the charts concerning BYETTA and VICTOZA, once in general the majority of the SOCs have much more number of reports in the U.S. than in the EU and the opposite happens with the *Neoplasms benign, malignant and unspecified* SOC.

As regards in the PT charts presented for each medicinal product, BYDUREON, LYXUMIA and TRULICITY do not present any neoplasm-related PT in the top 35 of the mostly reported PTs, and the same occurred for BYETTA, BYDUREON and VICTOZA in the U.S. charts. Concerning BYETTA and VICTOZA EU charts, the PT pancreatic carcinoma occupies the 3rd and the 2nd places of the mostly reported ADRs, respectively. Beyond this, other PTs related to the occurrence of neoplasms are presented in the top 35 of the mostly reported ADRs for both medicinal products which are: pancreatic carcinoma metastatic (15th and 13th), metastases to liver (18th and 31st), thyroid cancer (23rd and 28th), adenocarcinoma pancreas (31st and 25th) and papillary thyroid cancer (26th – for VICTOZA only).

Regarding the controversy of whether GLP-1–based therapy can increase the risk for specific malignant disease like pancreatic carcinoma and thyroid cancer*, Nauck M et al*, concludes that apparently there is neither firm evidence in favour of this hypothesis nor evidence strong enough to rule out any such increased risk based on results available at present [76]. Up to date, the FDA and the EMA have not reach a final conclusion regarding the possible association between the occurrence of cancers and the use of these medicinal products. FDA still recommends specific monitoring of medullary thyroid cancers in patients on GLP-1R agonists therapy [65].

On the basis of the aforementioned, it may be concluded that the nonclinical data are in accordance with the post-marketing information, as well as, to the assessments performed by the authorities. Regarding the pancreatic cancer, the only medicinal product for which this events was not considered a potential risk in the EU was VICTOZA. Nevertheless, and as identified, a thorough assessment was made and this medicine was specially evaluated, and as a consequence some updates were performed. Thus, probably the inclusion of pancreatic cancer as a safety concern was already made. Regarding medullary thyroid cancers, these are considered a potential risk for all medicinal products, therefore it is concluded that the safety concern is correctly addressed.

NERVOUS SYSTEM DISORDERS SOC

Terms that have a basis in a central nervous system disorder are linked primarily to SOC *Nervous system disorders*.

Despite not having been identified as safety concern associated with this therapeutic class, the *Nervous systems disorders* SOC appears in the top 10 of the most prevalent SOCs for all the medicinal products both in the EU and in the U.S.. Comparing the EU and the U.S., in the U.S. this SOC was more prevalent in all applicable medicines than in the EU. Continuing the comparison, but now concerning to the exenatide-containing medicinal products, BYDUREON demonstrates a higher prevalence in this SOC than BYETTA.

Among the 35 ADRs mostly reported, in the EU and/or in the U.S., it is possible to find some PTs concerning this SOC, for instance dizziness, headache, tremor and loss of consciousness.

In the published literature it is stated that animal studies have demonstrated that agonists of the GLP-1R (for instance, liraglutide) were able to cross the blood brain barrier following peripheral administration, and peripheral administration of GLP-1 suppressed food intake over the dependent and independent pathways of the vagus nerve, resulting in direct action in the brain GLP-1R in the central nervous system [65, 79]. Therefore, the occurrence of events related to the SOC *Nervous system disorders* are expected.

GLP-1R agonists have also been shown to exert a neuroprotective role in rodents with Alzheimer's and Parkinson's disease. Preclinical studies demonstrated that exendin-4 decreased glutamate beta-amyloid peptide, preventing apoptosis in rat hippocampal neurons

in culture. Both glutamate and beta-amyloid peptide is involved in neurodegeneration process [65]. The incidences of Alzheimer's disease and Parkinson's disease are increased in people with T2DM, suggesting a relationship between neuronal cell death and insulin dysregulation. The presence of hippocampal atrophy is also increased in people with T2DM (compared with control subjects) and appears to be correlated with poor glycaemic control and marked glycaemic fluctuation. Use of GLP-1R agonist therapy in people with T2DM was negatively associated with hippocampal atrophy, suggesting that this approach may exert novel treatment possibilities for diabetic encephalopathy [79]. By limiting hippocampal atrophy in people with T2DM, it is suggested that GLP-1R agonists may prove to be a valuable therapeutic agent for the future treatment of neurodegenerative diseases. Large studies are currently underway to test the effect of liraglutide or exenatide treatment, both in comparison to placebo, on brain inflammation and neuronal damage in people with Alzheimer's disease [79].

RENAL AND URINARY DISORDERS SOC

There is some evidence that GLP-1R agonists have a protective role in diabetic nephropathy. However, there are also associations of GLP-1R agonists with acute kidney injury. Exenatide is eliminated by renal mechanisms, and it is not recommended for use in patients with severe renal impairment or end-stage renal disease. In 2009, the FDA approved revisions to the drug label for exenatide to include information on post-marketing reports of altered kidney function. Main adverse effects of GLP-1R agonists include nausea and vomiting, which may result in decreased fluid intake and fluid loss, which can potentially lead to acute renal failure. Liraglutide is not eliminated renally, and mild renal impairment has not demonstrated a significant effect on its efficacy or safety, although there have been case reports of acute kidney injury with use of liraglutide in patients with moderate to severe renal impairment. Albiglutide once weekly was studied in a phase 3 trial compared to sitagliptin in patients with renal impairment and was found to be superior with similar tolerability. Of note, albiglutide does not require renal elimination or any dose adjustments for renal impairment. Dulaglutide also does not require any renal dose adjustments [58, 59, 65].

In the EU, acute renal failure/impairment was associated to the use of BYETTA, BYDUREON and LYXUMIA. For the first two this concern was classified as important identified risk and for the last one it was classified as important potential risk.

In the U.S. renal impairment was also considered a safety concern for BYDUREON. For ADLYXIN the occurrence of renal impairment in patients with severe GI reactions is also considered a safety concern. Regarding TANZEUM and TRULICITY, the addressed risk corresponded to the worsening of renal function precipitated by dehydration due to product related GI adverse reactions.

Concerning to the post-marketing data presented during this work, it is possible to observe that *Renal and urinary disorders SOC* has considerably high prevalence, as it is encompassed within the first 10 SOC mostly reported for all GLP-1R agonists, apart from BYDUREON and EPERZAN, for which there is no relevant post-marketing information.

As presented in Chart 11 and reflected in Table 20, Renal *and urinary disorders* SOC has major number of reports for BYETTA than for BYDUREON.

Additionally, this SOC is most prevalent in the EU than in the U.S. for BYDUREON. In contrast, for VICTOZA and for BYETTA the major prevalence occurs in the U.S..

Acute kidney injury and renal failure were the two PTs mostly reported related to this SOC. For Byetta both PTs were presented in the top 15 of the mostly reported ADRs in the EU, but not in the U.S.. TRULICITY also presented both PTs in the top 20 of the mostly reported ADRs, whereas LYXUMIA only presented acute kidney injury. BYDUREON did not presented any PT regarding this SOC among the top 35 of the mostly reported ADR.

As observed above, renal conditions may be associated with the use of this therapeutic class medicinal products. This was identified in the pre-marketing phase and it was corroborated in the post-marketing.
The most probable mechanism for this occurrence is nausea and vomiting, which if prolonged may result in dehydration, and severe dehydration leads to falling blood pressure, reduced perfusion of the kidneys and may cause acute renal failure. Those with compromised renal function, whether because of pre-existing vascular disease or because of a reduced number of functioning nephrons, are less able to compensate for acute dehydration, and are therefore at increased risk of acute renal failure [58].

This safety concern is correctly addressed by all medicines, therefore no any other action might be suggested at this time.

OTHER SAFETY CONCERNS

Late stage microvascular eye complication is an important identified risk for VICTOZA, in the EU. However, the post-marketing the occurrence of eye-related conditions is low as well as the prevalence of the *Eye disorders SOC.*

Teratogenicity is an important potential risk for LYXUMIA. Nevertheless, it is not corroborated by the post-marketing data, as no reports were identified in the *SOC Congenital, familial and genetic disorders*.

EPERZAN presents pneumonia as important identified risk and hepatotoxicity and foetal and neonatal developmental toxicity as important potential risk. Nevertheless, no conclusion related to these risks may be provided as these risks were only identified for this medicinal product and no relevant post-marketing safety information is available for EPERZAN.

LIMITATIONS

During the elaboration of the present work, several limitations were detected and faced on.

The major limitation was to acquire post-marketing information related to the U.S. market, as no public databases are accessible now. The database used to elaborate the present work only provided data until the third quarter of 2012. Therefore, after this date no information regarding the post-marketing reports are presented. As TANZEUM, TRULICITY and ADLYXIN were only approved after 2013 regarding the U.S. market is presented for them. This situation did not allow a complete analysis and comparison between the EU and the U.S. reporting profile. Additionally, the information presented for BYETTA, VICTOZA and BYDUREON if also incomplete and the reporting profile could be changed since 2012.

Other limitation was the absence of post-marketing data for EPERZAN in the EU database. As it was possible to see in the previous section, very scarce information was available for this medicinal product. Thus, it was not possible to make any conclusion regarding the reporting profile of this medicinal. Thus, it was not possible to know if the most reported ADRs in the post-marketing environment met those safety concerns identified in the pre-marketing phase. Moreover, for this medicinal product pneumonia, hepatotoxicity and foetal and neonatal developmental toxicity were identified as safety concerns by the clinical studies. These concerns were not considered for any other medicinal product belonging to this therapeutic class, and so no conclusion was made regarding the prevalence of these risks.

The data concerning the post-marketing reporting presented in the charts, in the RESULTS section, were collected from public databases which compiled the information of the total number of reported cases and presented them in chart and table format. One of the considered approaches was to try to normalize this data on the basis of total volume of sales, i.e. by the number of volume of sales it was possible to normalize the information per million of inhabitants, getting a more accurate basis for comparison of the occurrence of the reactions. Nonetheless, it was not possible to know the sales volume of such medicinal products and, thus, this normalization of data was not possible.

Conclusion/Final remarks

The main goals of the present work were drawing a safety profile for GLP-1R agonist and conclude on the need and/or opportunity of adapting the RMP to the new markets. Throughout this process, it became clear that the occurrence of adverse reactions was associated both to the pharmaceutical formulation of the medicinal products and to their mechanism of action. In general, the adverse reactions were similar among all the medicinal products under evaluation. Ultimately, and although there are some areas of special concern which require further and thorough analysis (namely the occurrence of CV adverse effects and thyroid or pancreatic cancers), it was concluded that all the safety concerns are being very well monitored and followed either by the EMA/FDA or by the Marketing Authorisation Holders (MAHs). No additional minimisation measures, other than those already defined and implemented, seem to be necessary, and, therefore, the RMPs do not need to be updated.

The GLP-1R are found throughout the body, including in the CV system, therefore providing a larger field to relevant metabolic influences such as diabetes and vascular complications. Specific receptors have been identified for G-protein coupled GLP-1 in tissues of the GI tract, pancreas, cardiac myocytes, liver, lung, blood vessels including the endothelium of the coronary artery, macrophages, peripheral nerves and the central nervous system [65].

GLP-1R agonists are effective agents for the treatment of T2DM, offering many advantages over other agents, including weight loss, potential β-cell protection and low risk of hypoglycaemia. They also have positive benefits on CV parameters, including reductions in blood pressure, lipids and body weight. Although long-term safety data is unavailable due to the short duration of time that these agents have been on the market, future studies will provide guidance to practitioners on the appropriate choice of agents to mitigate risk, including CV risk. Overall, GLP-1R agonists are effective and innovative agents for patients with T2DM and other chronic conditions, who are either uncontrolled or intolerant to first-line metformin therapy [59, 65, 79, 80].

Throughout the development of this project some limitations were detected. These limitations did not allow to perform a complete comparative analysis neither between the EU and the U.S. data, nor between all the medicinal products under analysis, as for EPERZAN no sufficient EU post-marketing data was available. Additionally, the normalization of the data presented in the charts was not possible as well.

Despite the referred limitations, the following conclusions have high significance and they are also corroborated by the scientific published literature.

In a global manner, the relevant safety information identified in the nonclinical phase was assessed and observed during the clinical phase. The results obtained from all the nonclinical and clinical studies were resumed in the RMP, in which the safety concerns were identified and classified as well as in which the plan for minimisation the risks is described. When observing the post-marketing data, collected from the public databases of adverse reactions reports, it was realized that, although some exceptions, the risks identified previously are the ones mostly reported.

In general, the safety concerns identified for each GLP-1R agonist are similar to the safety concerned identified to the others GLP-1R agonists.

Regarding the European and the U.S. data several discrepancies were identified, namely what concerns to the malignancies occurrence. For example, in the post-marketing U.S. data, there was no cancer-related PTs reported within the top 35 of the mostly reported ADRs, whereas in the EU these reactions have high prevalence for some medicinal products.

On what regards to the occurrence of the identified adverse reactions with the mechanism of action, it was possible to state that they were closely linked. The concerned effects occur in areas where GLP-1R exists.

The occurrence of adverse reactions is also associated to the pharmaceutical formulation of the medicinal products, for instance long acting agents have more reports of injection site reactions.

It's worth noting that some adverse events could be considered a beneficial outcome in some circumstances. This is what happens to the "rapid weight loss", which was at the beginning identified as an identified risk for BYETTA and BYDUREON but not for the other medicines. This event had turned up into another indication for another medicinal product already approved for weight loss in patients without T2DM.

There are some areas of special concern which require further and thorough analysis, namely the occurrence of CV adverse effects and thyroid or pancreatic cancers. However, all safety concerns are very well monitored and followed either by the EMA or by the MAHs, which have in project and in progress several safety studies to well characterise both the important risks and the missing information identified in the RMPs.

As final conclusion, the safety profile of GLP-1R agonists remain unchanged after this evaluation and no new additional minimisation measures seems necessary.
Moreover, GLP-1R agonists show broad metabolic effects, far beyond the glycaemic control, and represent effective therapies for T2DM. Further benefits on metabolism are being discovered, as new trials come out. The next few years are expected to bring relevant new data regarding extra glycaemic effects of GLP-1R agonists. [65].

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